PROVISIONAL PROGRAM

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

Place of Meeting: Claridge Hotel, Atlantic City

Friday Morning, April 30, 1948 9:00

1. Infectious Mononucleosis and Infectious Studies Bearing on Certain Resemblances a[nd] ences. J. Edward Berk, Harry Shay and (by invitation) Joseph A. Ritter and Herman Siplet, Philadelphia. (10 minutes)

2. Studies on the Removal of Bromsulphalein from the Blood. Franz J. Ingelfinger and (by invitation) S. E. Bradley, A. I. Mendeloff and P. Kramer, Boston. (10 minutes)

3. Combined Liver Biopsy and Liver Function Studies in 120 Cases of Cholelithiasis and 32 Cases of Peptic Ulcer. (Proven Operated Cases) John G. Mateer and (by invitation) Frank W. Hartman, James I. Baltz, Laurence S. Fallis and Arthur B. McGraw, Detroit. 10 minutes Discussion by Leon Schiff

4. Surgical Procedures in Pronounced Portal Hypertension. A. H. Blakemore, New York (by invitation). 15 minutes Discussion: L. K. Ferguson, Philadelphia

A Symposium

Clinical and Pathologic Sequelae of Acute Hepatitis

5. Physiologic Aspects of Sequelae. Laurence W. Kinsell, Oakland, California (by invitation). 10 minutes

6. Clinical Aspects. Richard B. Capps, Chicago, Illinois (by invitation). 10 minutes

7. The Validity of Laboratory Evidence of Sequelae. Henry J. Tumen and (by invitation) Edwin M. Cohn, Philadelphia. 10 minutes

8. Pathologic Concepts of Sequelae of Acute Hepatitis. Max M. Strumia, Bryn Mawr, Pennsylvania (by invitation). 10 minutes

Discussion: Leon Schiff, Cincinnati, David H. Rosenberg, Chicago and Frank W. Hartman, Detroit

Friday Afternoon, April 30, 1948 2:00 P. M.

9. Hypertrophy of Brunner's Glands Simulating Duodenal Polyposis. Thomas A. Johnson and (by invitation) William Erb, Philadelphia. 10 minutes

10. Enterocolitis as a Post-Operative Complication and Its Significance. Abraham Penner and (by invitation) Leonard Druckerman and Ralph Colp, New York. 10 minutes

11. The Effects of Certain So-Called Antispasmodics on Human Intestinal Motility. J. Arnold Bargen and (by invitation) E. Leonard Posey and Charles Code, Rochester, Minnesota. 10 minutes

Discussion: Julius Comroe, Philadelphia (by invitation), and Stewart Wolf, New York

12. Digestion and Absorption in a Woman with Eighteen Inches of Small Intestine. Theodore L. Althausen and (by invitation) Kahn Uyeyama and Roger G. Simpson, San Francisco. 10 minutes

13. Protein Metabolism in Chronic Ulcerative Colitis ington, Washington, D. C. (by invitations

L. Althausen, San Francisco

14. The Surgical Care of Complications of Ulcerative Colitis. L. Kraeer Ferguson, Philadelphia. 10 minutes

15. Treatment of Non-Specific Ulcerative Colitis for One Year with Extracts of Intestinal Mucosa. J. Earl Thomas and (by invitation) M. H. F. Friedman and B. F. Haskell, Philadelphia. 10 minutes

16. Pancreatic Function in Chronic Pancreatitis as Measured by Chemical Analysis of (1) Duodenal Contents Before and After Stimulation with Secretin, and (2) Feces for Total Solids, Fat and Nitrogen. Manfred W. Comfort and (by invitation) George R. Dornberger, Eric E. Wollaeger and Marschelle H. Power, Rochester, Minnesota. 10 minutes

17. Pancreatic Function (Studies with Secretin). David A. Dreiling, New York (by invitation). 10 minutes

18. The Effect of Demerol upon the Sphincter of Oddi in Man. George S. Bergh and (by invitation) R. W. Utendorfer, Minneapolis, Minnesota. 10 minutes

19. Acute Cholecystitis: Correlation Between Mortality and Bacteriology. Leon Goldman, San Francisco. 10 minutes

20. EXECUTIVE SESSION

For Senior and Active Members Only

IN MEMORIAM

Thomas S. Pilcher, Brooklyn

John L. Kantor, New York

21. Friday Evening—Annual Dinner

Banquet Speaker—to be announced

Presentation of the 1948 Julius Friedenwald Medal to Dr. Franklin W. White, Boston

Saturday Morning, May 1, 1948 9:00 A. M.

22. Presidential Address

Henry L. Bockus, Philadelphia

23. Peptic Ulcer in Infancy. Report of a Case with Hemorrhage and Perforation. Russell S. Boles and (by invitation) Bernard Margolis and Marie Valdes Dapena, Philadelphia. 10 minutes

24. The Effect of Insulin Hypoglycemia on Gastric Secretion in Duodenal Ulcer Patients and Normals. Asher Winkelstein and (by invitation) Manfred Hess, New York. 10 minutes

25. Observations on Intractable Nocturnal Secretion in Patients with Peptic Ulcer. Joseph B. Kirsner and (by invitation) Erwin Levin, Chicago

26. The Comparative Buffering Capacity of Intact and Pre-digested Protein. Jerome S. Levy, Little Rock, Ark. 10 minutes

Discussion: J. Edward Berk, Philadelphia

(Continued on next page)

VOLUME 10, NUMBER 3

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

WALTER C. ALVAREZ, *Editor*

A. C. IVY, *Assistant Editor*

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BALTIMORE, MD.

PROVISIONAL PROGRAM, (*Cont.*)

27. Results in Treatment of 330 Mann-Williamson Ulcers. David J. Sandweiss and (by invitation) Harry C. Saltzstein, John N. Hammer and Edward J. Hill, Detroit. 10 minutes

28. Oral Treatment of Chronic Duodenal Ulcer With an Extract of Pregnant Mares Urine (Preliminary Report). Z. T. Bercovitz, Robert C. Page and (by invitation) Reid R. Heffner, New York. 10 minutes

29. A Study of Gastric Ulcer. Sara M. Jordan and (by invitation) Francis H. Smith, Boston. 10 minutes

30. Studies on Roentgen Irradiation in the Therapy of Peptic Ulcer. Walter L. Palmer and (by invitation) William E. Ricketts and Anna Hamann, Chicago. 10 minutes

31. Benign Stricture of the Esophagus. Edward B. Benedict and (by invitation) Richard H. Sweet, Boston. 10 minutes

32. Experimental Production of Cardiospasm in Human Subjects. Stewart Wolf and (by invitation) Thomas P. Almy, New York. 10 minutes

Saturday Afternoon, May 1, 1948 2:00 P. M.

33. Report of the Committee on Peptic Ulcer. David J. Sandweiss, Detroit, Chairman. 10 minutes

34. Report of Subcommittee on Vagotomy. Sara M. Jordan, Boston, Chairman. 10 minutes

35. Report of Subcommittee on Hormones. A. C. Ivy, Chicago, Chairman. 10 minutes

36. Report of Subcommittee on Psychosomatic Aspects of Ulcer. T. Grier Miller, Philadelphia, Chairman. 10 minutes

2:40 P. M. Panel Discussion on Vagotomy
H. L. Bockus, Moderator

37. Physiological Aspects of Vagotomy. J. Earl Thomas, Philadelphia. 8 minutes

38. Laboratory Procedures in the Study of Vagotomy. Franklin Hollander, New York. 8 minutes

39. Gastrointestinal Motility Following Vagotomy. Thomas E. Machella, Philadelphia. 8 minutes

40. Follow-up of Vagotomy Alone (Simple Vagotomy) for Ulcer. Francis D. Moore, Boston. 8 minutes

41. Follow-up of Vagotomy Plus Gastroenterostomy or Pyloroplasty for Ulcer. E. N. Collins and (by invitation) George Crile, Jr., Cleveland. 8 minutes

42. Follow-up of Vagotomy Plus Gastric Resection or Ulcer. S. Allen Wilkinson, Boston. 8 minutes

43. Follow-up of Vagotomy Alone (Simple Vagotomy) Ultimate Results. Lester R. Dragstedt, Chicago. 8 minutes

44. Ultimate Results of Vagotomy. Julian M. Ruffin, Durham. 8 minutes

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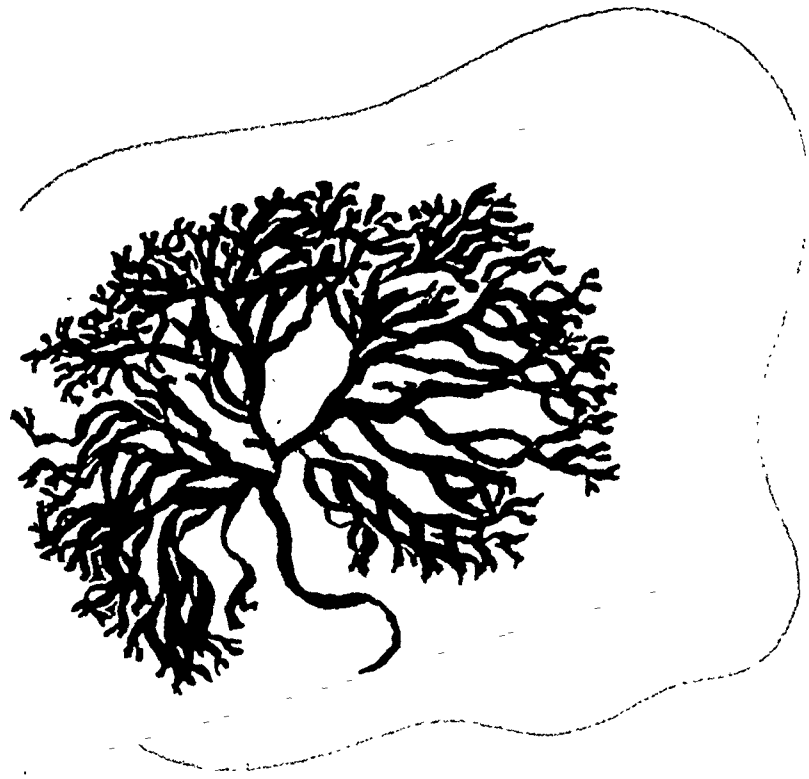

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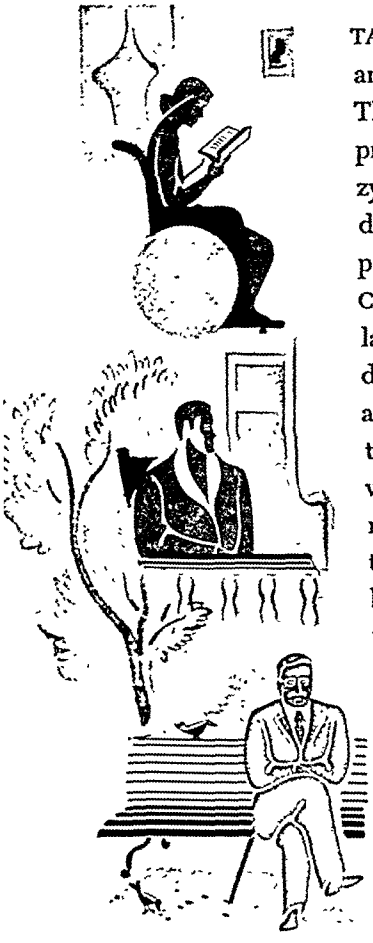

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MEDICAMENTA VERA

ERRATA

In the article by Dible, McMichael & Sherlock, ("Gastroenterology 1947, *6*, 736) the line charts submitted by the authors were omitted. The data concerning bilirubin concentrations in bile were contained in these charts, copies of which can be made available on application to the authors.

P. 739, line 10 from bottom: "Tubules" should read "lobules".

P. 740, line 8 from bottom: "This could be felt" should read "This organ could be felt".

Fig. 4: The right side of the picture should be at the top.

P. 742, line 22: "June 30, 1943" should precede the sentence beginning "Blood urea" on the following line.

P. 744 line 23: For "did not show" read "did show".

P. 744, line 26: For "which" read "who".

P. 745, line 9: "Recognitions" should read "recognition".

P. 745, line 12: "a constant" should read "constant".

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

VOLUME 10 *March 1948* NUMBER 3

LATE MANIFESTATIONS OF EPIDEMIC INFECTIOUS HEPATITIS[1]

WADE VOLWILER, M.D., AND CAPT. JOSEPH A. ELLIOTT, JR., M.C., A.U.S.

From the Medical Services of the Massachusetts General Hospital, Boston, and of the Murphy General Hospital, U. S. Army, Waltham, Massachusetts

Accurate and complete data concerning late manifestations of epidemic infectious hepatitis are few. In most reports to date laboratory tests have been incomplete or poorly chosen, and histologic observations have been lacking. Without examination of biopsy or autopsy material the true state of hepatic histopathology is uncertain; purely speculative conclusions, based upon the physical examination and liver function tests, may be erroneous.

For many years it has been recognized by clinical observations alone that in occasional patients epidemic hepatitis ("catarrhal jaundice") may pursue a prolonged, smoldering, chronic course (1, 2). This uncommon variant from the usual pattern has recently been reemphasized (3, 4, 41). Three such cases with complete laboratory studies, in two of which biopsies were obtained by surgical laparotomy six and nine months after the onset of the disease, are described by Neefe (5). Flood and James (6) report twelve patients in whom needle biopsies showed persisting, active inflammation 73 to 761 days after the beginning of the hepatitis. In 40 individuals, clinically thought to be cases of delayed convalescence, peritoneoscopic biopsies obtained 100 to 510 days following the onset of acute disease are described by Mallory (7); 15 of these showed definite histologic signs of active hepatitis.

Evidence in the form of scattered case reports accompanied by histologic observations has accumulated to indicate that epidemic infectious hepatitis may rarely produce progressive fibrosis of the liver with reparative nodular regeneration resulting in the clinical picture of cirrhosis (8, 9, 10). This end-stage pathologic pattern is usually considered to be that of post-necrotic scarring with nodular hyperplasia ("toxic cirrhosis"), though evidence that an occasional patient may develop a biliary type of cirrhosis is presented by Watson and Hoffbauer (11). Biopsies demonstrating the development of fibrosis during so-called arsenical hepatitis have been described (8, 9, 10); it is possible that most of the patients in these instances were primarily victims of syringe-

[1] Research Fellow of the American Gastroenterological Association for 1947.

transmitted serum hepatitis (12), the infective agent of which is closely akin to that of epidemic infectious hepatitis (13).

Persisting mild icterus without other abnormal signs or symptoms has been reported by several investigators (14, 15, 16) as a sequel to infectious hepatitis. Biopsies on two such individuals are mentioned by Flood and James (6), but to our knowledge, no group has been presented in detail after investigation by a complete battery of present-day, accepted tests of hepatic function and also by liver biopsy.

This report attempts to correlate clinical findings with laboratory data and liver biopsy histology in various late phases of hepatitis.

MATERIAL

Thirteen Army and civilian patients have been selected for case presentation. Nine of the thirteen had persisting active hepatitis proven by biopsy 4 to 42 months after the onset of jaundice in the initial acute illness;[2] the remaining four had shown continuous, mild, clinical icterus 18 months to 21 years following an illness typical of epidemic infectious hepatitis.

METHODS

Fasting blood samples were used in all tests. The data presented and the procedures described are those of the chemistry laboratory of the Massachusetts General Hospital.

Serum bilirubin was determined in the Evelyn photoelectric colorimeter by the method of Malloy and Evelyn (17). Values greater than 0.4 mg. per cent for the direct reacting fraction read at 30 minutes are regarded as abnormal. For the convenience of our laboratory routine, the 30 minute reading was used in preference to the recently advocated 1 minute reading of the direct-reacting fraction (18). It is believed that in the patients here reported the data obtained by the older method provides adequate information regarding disturbance in bilirubin excretion. The maximal normal value for total serum bilirubin is considered to be 1.0 mg. per cent.

Bromsulfalein retention was measured in the Evelyn photoelectric colorimeter on a blood sample drawn 45 minutes after the intravenous injection of 5 mgm. of dye per kilogram of body weight; in one case, as noted, a dose of 2 mgm. per kilogram body weight was given and the blood sample drawn in 30 minutes. Retention of the dye up to 5 per cent is considered to be within normal limits. The essential details of the method are as follows: A 565 mμ filter is used; 1 ml. serum is diluted to 10 ml. with isotonic saline solution. After obtaining a "center setting" 2 drops of 20 per cent sodium hydroxide are added. The tube is well shaken, and the readirg immediately obtained. The instrument is calibrated with known dilutions of bromsulfalein.

[2] The term chronic, as previously used by Barker, Capps and Allen (4) and by Neefe (5), is herein applied to such prolonged active hepatitis.

Serum total protein, albumin, and globulin were measured according to the method of Peters and van Slyke (19). Normal values for total protein lie between 6.5 and 8.0 grams per cent; for albumin, between 4.5 and 5.5 grams per cent; and for globulin, between 1.5 and 3.0 grams per cent.

The *cephalin-cholesterol flocculation* test was performed according to the directions of Hanger (20) with the modifications suggested by Neefe and Reinhold (21). "Difco" reagent was used. Readings up to 2 plus in 48 hours were considered normal.

The *thymol turbidity test* was carried out according to the technique of Maclagan (22) with certain modifications. The buffer used was prepared as directed but the pH of this solution, with our reagents, is about 7.65 rather than 7.8 as reported by Maclagan. Readings were made in the Evelyn photocolorimeter using a 620 mμ filter 30 minutes after the addition of 0.2 cc. of serum to 12 cc. of buffer. The colorimeter was standardized with Evans blue dye T-1824 as suggested by Kunkel and Hoagland (23). Values over 4 units are considered abnormal.

The *thymol flocculation test*, devised by Neefe (5), was read 24 hours following the determination of the thymol turbidity.

The *prothrombin clotting time* was carried out by the method of Quick (24).

Serum alkaline phosphatase was determined by the technique of Bodansky (25). Values between 2.0 and 4.5 units are considered normal.

Urine urobilinogen excretion in 24 hour urine collections was determined quantitatively by the method of Schwartz, Sborov and Watson (26). Values less than 3.0 mgm. are normal.

Fecal urobilinogen was determined quantitatively in Cases 10 and 11 on four-day stool collections by the method of Schwartz, Sborov and Watson (26).

The *erythrocyte sedimentation rate* was determined on heparinized blood by the method of Rourke and Ernstene (27). Normal values are considered to be those of less than 0.35 mm. per minute.

The *position of the palpable liver edge* is expressed as the distance in centimeters of the lower border of the right lobe below the costal margin in the mid-clavicular line on deep inspiration. Hepatic enlargement was considered to be present when this measurement exceeded 2 cm. if, during quiet respiration, the upper border of percussable liver dulness in the right mid-clavicular line anteriorly lay between the fifth and sixth ribs.

Liver biopsy was performed in all cases with the Iversen-Roholm needle as described by Volwiler and Jones (28). The tissue obtained was fixed immediately in Zenker's fluid.

RESULTS

The liver function data obtained at the time of biopsy are listed in table 1. These patients may be, for convenience, divided into three groups: (1) those in whom biopsy showed persisting active inflammation without fibrosis; (2) those in whom biopsy showed persisting active inflammation and fibrosis; and (3) those in whom liver biopsy and liver function tests were normal but who remained icteric.

Group 1 (Cases 1–7). The seven members of this group all complained of periodic easy fatigability, malaise after mild exertion, and anorexia. Occasional right upper quadrant abdominal discomfort was noted by three (Cases 2, 5 and 6), and nausea by three (Cases 1, 2 and 7). While physical activity was restricted to bed rest with a few hours daily in a chair, most of these symp-

TABLE 1

CASE NO.	TIME SINCE ONSET	POSITION LIVER EDGE†	PALPABLE SPLEEN	SED. RATE	BSP % RETENTION	SERUM BILIRUBIN	TOTAL PROTEIN	ALB.	GLOB.	CEPH. FLOC.	THYMOL		ALK. PHOSPHATASE	URINE UROBILINOGEN
											Turb.	Floc.		
Group 1. Persisting active inflammation by biopsy														
1	4 mo.	—	—	0.43	12	0.5/1.2	7.62	5.06	2.56	0/0	2.8	0	2.0	
2	4½ mo.	3	—	0.36	17	0.4/0.6	8.26	5.98	2.28	0/0	2.8	0	2.6	Normal
3	5 mo.	—	—	0.63	4	0.3/0.7	7.37	5.00	2.37	3+/3+	11	4+	2.1	
4	9 mo.	5.5	+	2.5	14	0.5/0.7	8.18	4.96	3.22	0/0	3.0	0	18.6	Normal
5a	14 mo.	1.5	+	0.38	15	0.4/1.1	7.76	5.49	2.27	0/0	4.0	±	4.4	Normal
5b	20 mo.	1.5	+	0.63	43	0.3/0.7	7.76	5.58	2.18	0/1+	5.0	0	4.5	
6	39 mo.	2	+	0.15	14	0.4/0.7	6.83	4.83	2.0	0/0	1.5	0	2.7	
7	42 mo.	4	—	0.45	7	0.8/1.6	7.30	4.51	2.79	0/0	5.2	3+	1.8	
Group 2. Active inflammation and fibrosis by biopsy														
8	5 mo.	—	—	1.95	36	1.1/1.5	9.06	3.96	5.10	3+/4+	8.5	4+	8.6	3.0 mgm.
9	33 mo.	6	±	1.18	15*	0.7/1.0	8.22	4.87	3.35	±/1+	8.2	4+	13.7	
Group 3. Normal liver biopsies														
10	18 mo.	3	+	0.2	2	1.2/2.2	7.50	5.23	2.27	1+/1+	2.5	2+	2.0	
11	36 mo.	—	—	0.2	4	1.4/1.5	6.85	4.71	2.14	0/1+	1.2	0	2.5	Normal
12	7 yr.	1	+	0.1	5	1.5/2.6				1+/2+	1.0	0	2.5	Normal
13	21 yr.	—	—	0.2	4	1.1/1.7	7.56	5.24	2.32	0/0	3.0	0		

* 2 mgm.

† The upper border of percussable liver dulness was found in the "normal" position in all patients in whom measurements exceeding 2 cm. are recorded.

The prothrombin clotting time was normal in all cases. Fecal urobilinogen excretion per 24 hours was 210 mgm. in Case 10 and 115 mgm. in Case 11.

toms were minimal or absent; constant fatigue persisted. In Case 7, faint scleral icterus could be detected. Three patients had slightly enlarged livers, but only one (Case 2) had a tender liver edge. Splenomegaly was present in three. The bromsulfalein retention was abnormally high in all but one member of this group; the sedimentation rate was elevated in all but one. Cephalin flocculation tests, repeated on several occasions, were normal in all but one patient. The thymol turbidity and thymol flocculation tests were abnormal

in only two cases. Quantitative 24-hour urine urobilinogen determinations, when carried out, were normal. Case 2 repeatedly showed a high serum alkaline phosphatase.[3]

In Group 1, practically all portal areas observed in the biopsy sections contained an excessive number of mononuclear leukocytes, comprised chiefly of lymphocytes and histiocytes, frequently accompanied by scattered polymorphonuclear neutrophiles, eosinophiles, and plasma cells. All but one of the biopsies (that of Case 3) also contained small intralobular focal collections of lymphocytes and histiocytes. Parenchymal cells showing acidophilic coagulative necrosis were rare and identifiable in only three biopsies (Cases 4, 5 and 7). Occasional Councilman-like bodies were observed in Case 5. Otherwise the parenchymal cells appeared quite normal.

Group 2 (Cases 8 and 9). These two cases differed in their degree of symptoms and type of illness. Case 8 represented a rapid progression of the disease process during a five months' illness accompanied by persisting mild icterus, but with few symptoms; Case 9 had a smoldering hepatitis for 33 months with many symptoms but with only two short episodes of jaundice during the more acute phases of his disease. In both cases, most of the liver function tests were markedly abnormal; sedimentation rates were elevated; splenomegaly was absent. In Case 8 the liver was of normal size. The pattern of fibrosis seen in the biopsy specimens was strikingly different. Case 8 presented an example of subacute atrophy with nodular regeneration of parenchymal cells while in Case 9 the slight increase in fibrous tissue appeared to extend uniformly around the lobules. In both cases, active inflammation, typical of infectious hepatitis, was found in close association with the areas of fibrosis.

Group 3 (Cases 10–13). As was true of Cases 1–9, none of these four patients had had jaundice prior to their actue infectious hepatitis. Except for mild icterus, two of the group (Cases 11 and 12) had no other symptoms. The other two, in addition to jaundice, complained of periodic recurrence of easy fatigue and lack of energy. All four were leading lives of normal physical activity. Case 10 had at times periods of nausea and rare vague right upper abdominal discomfort; occasionally, following exercise, his slightly enlarged liver was tender to palpation. The spleen was enlarged in two of the group. In all four, the elevation of the serum bilirubin occurred in the direct reacting fraction though bilirubinuria could not be detected. The serum alkaline phosphatase was normal in the three cases in which it was determined. All other liver function tests, including the bromsulfalein, were normal; the sedimentation rates were also normal. A Graham test was normal in Cases 12 and 13,

[3] Previously this patient's extrahepatic biliary tract had been examined at laparotomy and found to be normal. His bones by x-ray examination and his serum calcium and cholesterol determinations were also normal.

and the duodenal bile sediment was normal in Case 13. Normal red blood cell fragility in hypotonic saline solutions and normal reticulocytes counts were found in all four of the group; and in Cases 10 and 11, the fecal quantitative urobilinogen determinations were within normal limits. The liver biopsy in each of the four patients revealed normal histology.

CASE REPORTS

The following case histories and biopsy reports are representative.

Group 1

Case 5. In July 1945 this 29 year old white Army officer developed anorexia, malaise, and tenderness over the lower sternum. His temperature rose to 103 F. and his urine became dark but there was no icterus. He remained in bed for one week and then returned to duty, only to have a recurrence of these symptoms in another five days. In September, following three similar episodes, he was hospitalized during a fourth which was accompanied by mild icterus of short duration. After six weeks in the hospital, he returned to duty, but had another exacerbation without jaundice and was rehospitalized. Following symptomatic recovery he was returned to the United States for separation, which occurred in December 1945. In February 1946, while on terminal leave, after a marked increase in physical exertion and the daily consumption of one or two cocktails, he developed generalized malaise and went to bed. His urine was dark but there was no jaundice. On February 24, he was admitted to the hospital as an ambulatory patient. Physical examination at that time was entirely normal except for slight right upper quadrant tenderness. He was made a bed patient in April because of a consistently abnormal bromsulfalein test, retention ranging between 10 and 20 per cent. While on bed rest, his symptoms were minimal or absent. He was discharged from the hospital in August to continue convalescence at home; the bromsulfalein retention was then 10 per cent. After an increase in physical activity his generalized malaise and right upper abdominal pain recurred, and he was readmitted to the hospital late in September 1946. His physical examination was unchanged from the previous one. The symptoms subsided rapidly on bed rest. The biopsy performed in October 1946 was described as follows: "The liver shows marked persistent peri-portal inflammatory infiltration and many foci of intralobular inflammation. There is moderate fat infiltration. No Councilman-like bodies are seen, and there is no evidence of a cirrhosis. *Diagnosis:* Active chronic epidemic hepatitis" (Fig. 1).

A second liver biopsy, obtained after another six months of semi-ambulatory convalescence, showed "evidence of persistently active hepatitis shown by fairly marked mononuclear infiltration of the portal areas with some tendency to the formation of lymphoid germinal centers, and also by focal necroses of liver cells of the acidophilic Councilman body type and small intralobular aggregates of inflammatory cells. There is also a moderate grade of coarse fat vacuolization which is not oriented in any particular part of the lobule. It is believed that this represents fat

storage rather than a manifestation of liver disease. The fibrous tissue in the portal areas is not definitely increased."

Comment. Except for one very brief icteric episode three months after the onset of the disease, this case is an example of prolonged hepatitis with multiple exacerbations, without jaundice, produced by increase in physical activity. Though the constant symptom pattern and the abnormal bromsulfalein tests suggested the correct diagnosis, histologic confirmation was necessary for conviction that a long, careful convalescent program should be enforced. An

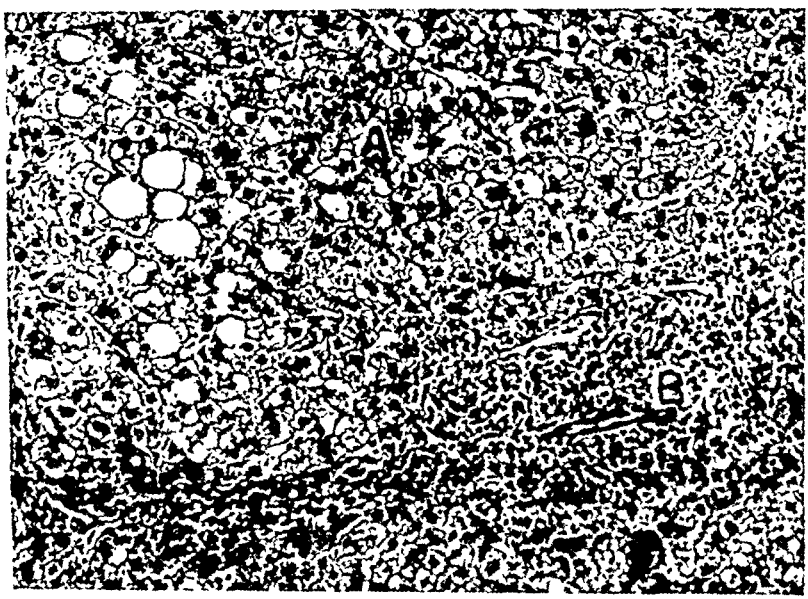

FIG. 1. CASE 5. NOTE INTRALOBULAR AGGREGATE OF LEUKOCYTES (a) AND PORTAL AREA LEUKOCYTIC INFILTRATE (b)

ideal regimen was not followed, and there was no essential change in the histologic pattern during the six months between biopsies.

Case 6. This 38 year old white Army medical officer first became icteric in March 1943 when he also noted nausea, anorexia, and pruritus. His icterus index rose to 50. After 3 weeks' hospitalization he was discharged back to duty as a surgeon. His icterus index subsequently remained between 6 and 15. With the increase in physical activity, however, he noticed a return of fatigue, nausea, right upper abdominal tenderness, and hepatic enlargement. In January 1944, during an upper respiratory infection, he had a return of all these symptoms; in November he had another exacerbation; and in December 1945, he was retired with a diagnosis of "cirrhosis of the liver". A renewal of symptoms while on terminal leave caused rehospitalization in January 1946 at which time a palpable, tender liver and a palpa-

ble spleen were found. Since that time his course has been one of remission and relapse, the latter usually related to an increase in physical activity. A liver biopsy in November 1946 was reported as follows: "There is a slight increase in lymphocytes in all portal areas although none shows any marked degree of infiltration. No intralobular changes are made out, except for a slight degree of fat vacuolization and two small collections of six to eight mononuclear phagocytes. The findings suggest a minimal persistent activity of epidemic infectious hepatitis."

Comment. In this patient the severity of the symptoms, consistently related to increase in physical activity, has been far more impressive than the usually equivocal physical examination and the slight but constant abnormality of the bromsulfalein test. At times the diagnosis of psychoneurosis has been chosen as an explanation for his prolonged illness. Cirrhosis was not present. The histologic abnormalities were minimal. Nevertheless, a diagnosis of persisting infectious hepatitis seems reasonable, based on the combination of (1) a typical symptom pattern, (2) a consistently abnormal bromsulfalein test, and (3) characteristic, though slight, histologic changes in the liver biopsy.

Case 7. In April 1942 this 33 year old white Army officer was captured by the Japanese on Bataan. During the next two years' imprisonment he had about 30 attacks of malaria; at no time did he receive suppressive atabrine. In September 1943, while interned at Dapecol, Mindanao, scleral icterus and an enlarged spleen associated with nausea and vomiting were first noticed. His symptoms were varied and he is unable to differentiate those of infectious hepatitis from those of malaria, beriberi and various tropical fevers. In June 1944, his jaundice, which had persisted in a mild degree, reached its highest peak while he was on shipboard on his way to Luzon after release from prison camp. This increase in jaundice coincided with an attack of malaria and was accompanied by nausea and vomiting. When, in November 1945, he finally reached a large general hospital he was still slightly jaundiced though by that time he was well nourished; his spleen was not palpable, but his liver was felt two fingers' breadths below the right costal margin on inspiration. A blood smear was negative for malaria; the sedimentation rate was elevated, and a 2 mgm. bromsulfalein test showed 12 per cent retention. Since his return to this country, he has been continuously hospitalized as an ambulatory patient. He has experienced recurrent episodes of marked fatigue, nausea and vomiting, usually precipitated by exercise. His appetite has continued to be poor. The liver biopsy of October 1946 was described as follows: "The portal areas uniformly show a moderate grade of lymphocytic infiltration, and nearly all of them also contain small numbers of eosinophiles. There is no significant bile duct proliferation or fibrosis. There are numerous focal collections of mononuclear cells in the intralobular sinusoids. The liver cells show a moderate degree of fat vacuolization, both coarse and fine, which is quite irregular in distribution. Very few necrobiotic liver cells can be identified. The findings are consistent with persistent infectious hepatitis of considerable duration."

Comment. Active chronic inflammation of infectious hepatitis may persist for several years without resulting in fibrosis. In this instance, the prolonged malnutrition and the numerous coincident infections were undoubtedly in part responsible for the long duration of the hepatitis, but a more stringent limitation of physical activity should have speeded convalescence. Though the liver was enlarged and histologically showed diffuse inflammation, it was at no time tender to palpation.

Group 2

Case 8. This 20 year old white field artilleryman was sent to the South Pacific in August 1945. At that time he began to take suppressive atabrine. In June 1946 he developed a cough, low-grade fever, generalized malaise, and anorexia; he lost approximately 15 pounds weight in a period of four weeks. He was hospitalized with a diagnosis of atypical pneumonia and improved rapidly under symptomatic treatment. Because it was noticed that his skin continued to be yellow despite the discontinuance of atabrine, liver function tests were done with the following results: urine urobilinogen was positive in a dilution of 1:50, cephalin flocculation was 4 plus in 24 hours, and total serum bilirubin was 3.8 mgm. %. After four weeks of hospitalization he was evacuated to this country as an ambulatory patient in September 1946. His symptoms at this time were minimal, consisting only of ease of fatigue and lack of energy; physical examination showed several spider angiomata; the liver and spleen were normal in size. A chest x-ray was normal, as were the Kahn, the quantitative Kahn, and the quantitative Wassermann tests. A serum Brucella agglutination test was negative. A liver biopsy was done in October 1946 and was reported as follows: "The specimen consists largely of areas of condensed fibrous tissue containing numerous bile ducts and inflammatory cells, scattered through which are liver cells, sometimes single, sometimes in small clusters. There are also a number of granulomatous foci containing epithelioid cells and an occasional giant cell. There are two larger islands of regeneration. The liver cells in these areas are very variable in size and staining reaction. The sinusoids contain small clusters of mononuclear cells. An occasional Councilman-like body is seen. *Diagnosis:* Subacute atrophy of liver, granulomata of undetermined etiology, and active inflammation consistent with persisting epidemic infectious hepatitis" (Fig. 2).

As evaluated by liver function tests, he failed to make any progress on complete bed rest and adequate diet. He was given two courses of intravenous human albumin, each consisting of 175 grams administered over a period of two weeks. Following each course his serum albumin rose and his globulin fell, while the total protein remained essentially at the same level. This effect, however, was transitory. In February 1947 the patient was transferred to a Veterans Administration hospital for continued convalescence. Two months later he was still slightly icteric, and tests of liver function were approximately the same as at the time the biopsy of the liver was performed.

Comment. As is frequently true in prolonged hepatitis, the symptoms and physical examination in this case did not indicate the severity of the existing liver pathology. The disease had progressed rapidly in spite of continuous, ideal care. Granulomata of the type observed in the biopsy of this patient are not infrequently seen during convalescent infectious hepatitis (29, 30), as well as in numerous other hepatic disorders; no other explanation of their presence in this instance could be found.

FIG. 2. CASE 8. MASSON STAIN SHOWING NODULE OF LIVER CELL REGENERATION (a) AND AREA OF ATROPHY (b)

Case 9. In January 1944 this 43 year old business executive had an illness typical of moderately severe infectious hepatitis with jaundice, anorexia, nausea, dark urine, pruritus, and marked malaise. The jaundice disappeared within one month, but marked weakness, anorexia, and malaise have continued. In August 1945 a six weeks' exacerbation of the disease occurred with the temporary reappearance of jaundice, dark urine, nausea, and pruritus. Constant vague symptoms have caused the patient voluntarily to remain a semi-invalid, and though during this time his diet has been of good quality, he has not regained the initially lost 10 pounds of weight. He has had an occasional cocktail. In October 1946, physical examination showed a well nourished man without scleral icterus, splenomegaly, spider angiomata, ascites, or peripheral edema; the liver was enlarged but not tender; laboratory data were essentially the same as those obtained 3 months previously; the liver histology from a biopsy specimen was described as follows: "The portal areas are uniformly conspicuous. They are slightly widened and the fibrous tissue is slightly increased. The portal areas are fairly densely infiltrated with inflammatory cells both mono-

nuclear and polynuclear. The latter include moderate numbers of eosinophiles. There is some tendency for infiltrate to invade the periphery of the lobules. Bile ductules are slightly increased in number. The lobular architecture is maintained and the central veins are not remarkable. There are a few collections of inflammatory cells within the lobule. The liver cells show no fat vacuolization. A surprising number of them show pyknotic nuclei without other evidence of degeneration. A rare Councilman-like body is found. In addition there are several small granulomatous foci of epithelioid and giant cells without caseation. These are, for the most part, in the portal areas, but one appears to be intralobular. The findings are

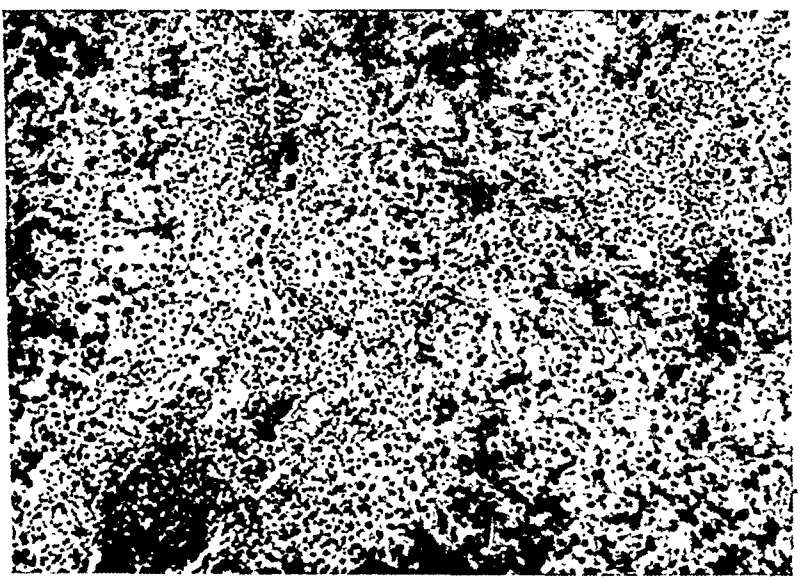

FIG. 3. CASE 9. NOTE MARKED PERIPORTAL INFILTRATION OF LEUKOCYTES

consistent with chronic persistent epidemic hepatitis. The granulomatous reaction is probably coincidental" (Figs. 3 and 4).

Comment. This patient illustrates the fact that in spite of fairly adequate care, hepatitis may continue for a long time and give rise to fibrous scarring. It is possible that needle sampling of the liver may give a false impression of the total amount and character of fibrosis actually present, but in this case the clinical picture and the laboratory findings also suggest a serious, progressing process.

Group 3

Case 10. During the last 2 weeks of May 1945 this 21 year old combat infantryman noted weakness, general malaise, and vague gastrointestinal symptoms of fulness after meals, heartburn, and periodic mild diarrhea and nausea. On June 5,

1945, jaundice, light colored stools and dark urine appeared, and lasted three and a half weeks; the liver was enlarged and tender. During the acute illness he was kept at bed rest and was given a high-caloric, low-fat diet supplemented daily with 20 brewer's yeast tablets. Symptomatic improvement was rapid, but because the icterus index remained elevated, the patient was transferred to another Army hospital for further convalescence. Here, except for lavatory privileges, he was confined to bed for an additional 3 months during which he was asymptomatic. Icterus indices ranged irregularly from 12 to 20, but bromsulfalein tests (2 mgm. dose with blood sample taken in 20 minutes) were normal. Since discharge from the Army in January 1946 he has been fully ambulatory at college; his diet has been high in

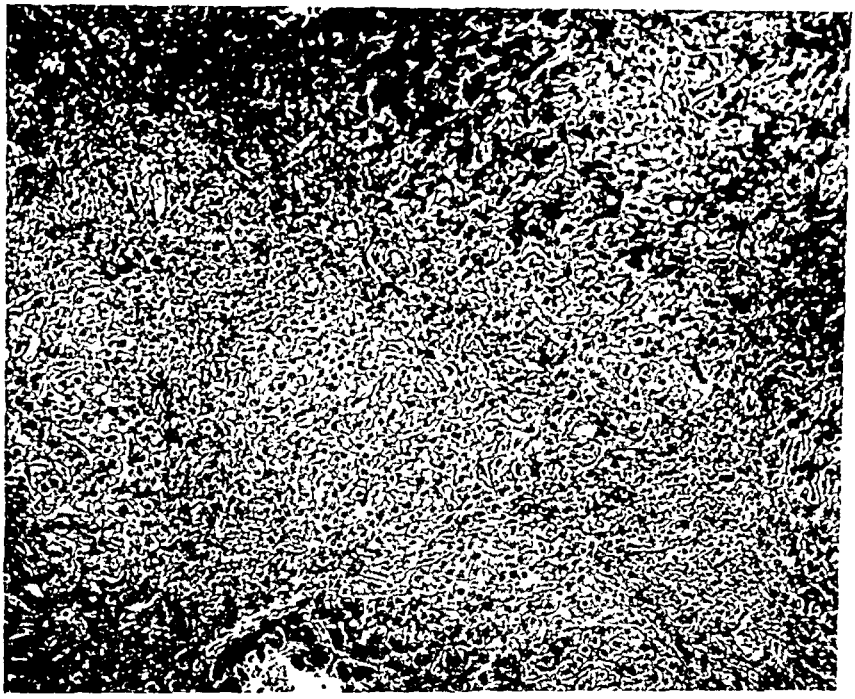

FIG. 4. CASE 9. MASSON STAIN DEMONSTRATING AN INCREASE OF PERILOBULAR CONNECTIVE TISSUE

calories and in protein, and he has abstained from alcohol. He has been examined every 3 months, and at each office visit mild icterus and splenomegaly have been apparent; the liver has remained palpable, and at times its edge has been very tender to palpation. Occasionally he has noted a return of his symptoms of easy fatigue, malaise, nausea, and right upper abdominal discomfort, but they have never been marked. Serial laboratory studies during the past 15 months have shown little variation. Biopsy of the liver was done at a time when the edge was tender to palpation; histologic examination of the specimen showed normal hepatic tissue.

Comment. Although constant mild icterus remains in this patient, it is believed to represent a selective hepatic dysfunction in the excretion of bile

pigment. The prognosis is considered to be excellent. This patient illustrates the fact that the finding of a tender, palpable liver edge following exercise does not necessarily indicate the presence of a persisting, histologically active hepatitis.

DISCUSSION

Certainty of a diagnosis of chronic, active infectious hepatitis is often impossible when it is made on the basis of clinical findings and liver fucntion tests without histologic confirmation. The foregoing cases, as well as those described by Neefe (5), substantiate this fact. The symptoms are usually minimal and vague; they differ little from those of patients whose various complaints persist long after the subsidence of an acute hepatitis but whose liver function by laboratory tests and whose liver substance by histologic examination prove normal. Accurate and complete data on a group of patients of the latter type have been presented by Sherlock (31). In the group we report physical signs were variable and of little assistance in making the diagnosis. Hepatomegaly was present in less than half the cases that showed persisting inflammation histologically; only one in that group had a liver edge tender to palpation. We, like Sherlock, have seen patients who, long after recovery from active hepatitis, present tenderness to palpation over the liver edge, particularly after exercise, in spite of the fact that their liver biopsies show normal histology. Persisting splenomegaly is not necessarily an index of active hepatitis; we have found, but are unable to explain, enlargement of the spleen lasting indefinitely after recovery in cases in which the liver biopsy specimen was entirely normal.

In our cases showing continued inflammation, no single liver function test was consistently abnormal; the bromsulfalein test provided the best laboratory clue to the correct diagnosis. It was normal in Neefe's three cases (5) and in a few of those reported by Flood and James (6). In contrast to Neefe's experience, the thymol flocculation test proved helpful in suggesting histologic activity in only two of our group. We have observed two patients, long recovered from hepatitis, who repeatedly have had a 2 or 3 plus thymol flocculation test at a time when the liver biopsy was normal. (Case 10 is one of the two.) Likewise, we have seen a few patients whose cephalin flocculation test remained 3 or 4 plus long after liver biopsy histology became normal. In all but one of our group of chronic hepatitis, the sedimentation rate was increased; this is in contrast to the usual finding of normal values in the acute phase of the disease. Neefe's experience with this test was similar to ours. Although the 24 hour quantitative urine urobilinogen determinations when carried out on our patients were within normal limits, Watson (42) has observed a case of histologically-proven persisting hepatitis in which an elevated urine urobilinogen excretion occurred as the sole abnormal liver function test.

The histologic evidence of persistent active hepatitis was conclusive in all of the cases in Group 1 and consisted chiefly of two types of abnormalities: (1) definite increase in mononuclear leukocytic infiltration of practically all portal areas observed in the biopsy section, more significance being attached to the presence of accompanying eosinophiles and plasma cells in this infiltrate than to the total number of lymphocytes; and (2) the presence of multiple small intralobular focal collections of histiocytes and lymphocytes. All biopsies showed the first type of change and all but one (Case 3) the second. Mallory (29), who had opportunity to examine a few individuals who met accidental deaths during the mild, subacute phase of epidemic hepatitis, found on postmortem study of multiple liver sections that nearly all portal areas contained an abnormally increased infiltration of mononuclear leukocytes. This bears out our belief that similar findings in a deep needle biopsy specimen adequately reflect a diffuse disease pattern.

As convalescence proceeds the intralobular inflammation undoubtedly slowly subsides to the point where, as emphasized by Neefe (32), only equivocal findings may be seen on histologic examination of the biopsy material. When accompanied by one or more abnormal hepatic function tests, such minor changes may be of clinical significance. Case 7 illustrates this point. Mild, continued impairment of one liver function test, however, may sometimes occur in patients showing normal biopsy histology and in such cases is probably of no clinical significance.

Leukocytic infiltrations of occasional portal areas are commonly observed in normal livers immediately beneath Glisson's capsule and in the area of the liver adjacent to the gallbladder. One must, therefore, guard against falsely interpreting as clinically significant such findings in a small surface biopsy obtained at laparotomy or by peritoneoscopy; the deep tissue sampling usually secured by trocar on this account may be of greater diagnostic help where chronic infectious hepatitis is suspected.

When definite histologic evidence of persisting chronic inflammatory changes is found, it is obvious that either the resistance of the patient has been less efficient than that of the average individual, or that the infective agent is unusually virulent. Such a patient should be protected by a prolonged, conservative regimen of adequate rest and proper diet with abstinence from alcohol in order to insure an eventual maximum degree of recovery. These therapeutic measures should be continued until liver function tests return to normal or until histologic evidence of active inflammation has disappeared. Too often ignorance on the part of the physician or impatience on the part of the patient allows too early an increase in physical activity which may prolong convalescence or even result, as has been reported (3, 29), in a fatal exacerbation of the previously mild, smoldering disease.

Fibrosis, when found on initial biopsy in association with the active inflammation of epidemic infectious hepatitis, is considered by Lucké (33) to have antedated the acute hepatitis. This interpretation cannot of course be disproven. However, when no previous history, signs, or symptoms of hepatic disease can be elicited from a formerly healthy, well nourished, non-alcoholic young adult, whose epidemic hepatitis has been prolonged, it seems more reasonable to ascribe such fibrosis to this virus infection. Focal scars may occur, of course, without being found by any method of liver biopsy. Small lesions of this type have been discovered by Sherlock (31) in patients who have recovered from infectious hepatitis. In such instances they result in no gross abnormality of hepatic function and appear to be of no clinical significance. The two cases of fibrosis we have reported present the clinical picture of progressive chronic cirrhosis, and we believe the etiology in each case was the infective agent of epidemic infectious hepatitis.

Cases 10 to 13 demonstrate that mild persistent jaundice alone is not a sufficient criterion for a diagnosis of chronic active hepatitis. The explanation for the continued icterus in such patients is purely speculative. In these cases, the elevation of the serum bilirubin was repeatedly found to be in the direct reacting fraction. We have subsequently seen one other case in which jaundice following typical infectious hepatitis was associated with a predominant elevation of the indirect reacting bilirubin; liver biopsy was normal in this individual also, and two similar cases with normal liver biopsies are reported by Welin (34). Rozendaal, Comfort and Snell (35) have stated that in the recovery phase of any hepatitis a shift to a predominant elevation of the indirect reacting fraction may at times occur. This phenomenon was observed by Kunkel, Labby and Hoagland (41) in seven patients recovering from virus hepatitis.

According to present-day conceptions of bile pigment metabolism, an elevation of the direct van den Bergh fraction should eliminate from consideration a hemolytic process and so-called constitutional jaundice (36). In our cases, excessive hemolysis as an explanation for the icterus is further ruled out by the normal reticulocyte counts, hypotonic saline fragility tests, and quantitative fecal urobilinogen determinations. Against jaundice due to common duct obstruction, evidence includes repeatedly normal serum phosphatase values, a normal Graham test in two cases, and a normal duodenal bile sediment in one case; none of the patients gave a history at all suggestive of cholelithiasis.

Jones (37) has offered a plausible theory for the persistent jaundice in cases of this type. He postulates that focal distortion of lobular architecture, due to attempts at histologic repair, may result in spotty, blind terminations of large bile ductules. Bilirubin excreted by normal liver parenchymal cells into such blind loops and regurgitated into lymphatics may conceivably produce an increase in serum concentration of the direct reacting component.

This persistence of hyperbilirubinemia appears to be of little significance in these cases, and the prognosis is probably excellent. In the past much importance has been attached to abnormal values of various modifications of the bilirubin tolerance test as a measure of hepatic functional impairment in similar patients (14, 15, 38, 39), but recent critical experience suggests its probable unreliability (40).

SUMMARY

Late manifestations of epidemic infectious hepatitis include: (1) prolonged mild hepatitis which may last for several years without significant scarring; (2) progressive hepatic fibrosis associated with similar smoldering inflammation; and (3) continuous mild jaundice with normal biopsy histology and without abnormal liver function tests.

Thirteen case examples of these three groups are presented with complete liver function data and with histologic descriptions of needle liver biopsies.

The difficulties encountered in establishing a diagnosis of persisting infectious hepatitis are discussed.

The laboratory tests most likely to reflect persisting active inflammation are the 5 milligram bromsulfalein test, the thymol turbidity test, the thymol flocculation test, and the erythrocyte sedimentation rate.

In cases of prolonged infectious hepatitis deep liver biopsies, such as may be obtained by trocar, are necessary for accurate evaluation of the state of the liver, and the histologic information obtained thereby is often essential to planning an intelligent therapeutic program.

Acknowledgment

We are indebted to Col. Harry A. Clark for permission to carry out this study and to Lt. Col. Ralph L. Cox, Major Francis E. Bruno, and Dr. Chester M. Jones for their assistance and encouragement. We are particularly grateful to Dr. Tracy B. Mallory for his descriptions and interpretations of the biopsy specimens and to Mrs. Klara Edwards, Mrs. Gladys Drummey, and Miss G. Margaret Rourke for technical assistance.

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PARACOLON BACILLI AS RELATED TO CHRONIC DYSENTERY SYNDROMES

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When a patient with protracted dysenteric complaints is found to harbor no commonly-recognized agent of disease, but a coliform microorganism not currently classified as an enteric pathogen, that patient may find correct diagnosis and adequate treatment indeed difficult to obtain. However, a careful antigenic analysis of the organism he harbors may reveal that it contains the same antigens which are found in the *Salmonellae* and *Shigellae.*

Much work has been done in the field of antigenic analysis by such investigators as Ferguson and Wheeler (5), Smith (13), Stuart (14), and Boyd (2). It has been shown by Luippold (8–9) that there is a relationship between antigenic composition and immunogenic properties of enteric organisms, although he could not state the full extent of this relationship nor the conditions governing any correlation between the two. He did determine, however, that there is a degree of cross-immunity operating between *Salmonella* organisms and *E. coli* organisms containing *Salmonella* antigens, and he believes that the evidence obtained from a study of the antigenic structure and immunogenic behavior of a paracolon organism in relation to the attributes of a previously-described and recognized enteric pathogen constitutes sufficient grounds for classifying the paracolon bacillus itself as an enteric pathogen. Harris and Harris (6) have discussed the probability of a relationship between chronic enteric infections, chronic hepatitis, and various nutritional disorders, and believe that it is possible for any pathogenic organism in the gastrointestinal tract to cause liver disease. Sieve (12) recently reported infection as the chief etiological factor in 60% of a series of 200 cases of nutritional disorders.

This report covers several case records indicating what may be a significant relationship between paracolon bacilli having *Salmonella* or *Shigella* antigens, and certain chronic diseases. It appears from this investigation that some patients harboring paracolon bacilli present a history and clinical syndrome which is suggestive of chronic dysentery. This syndrome was sufficiently clear-cut in 18 suspected cases to result in isolation and identification of 16 strains of paracolon bacilli, most of which contained antigens of recognized pathogenic organisms. Detailed case reports are presented of four out of five patients who were given streptomycin therapy to eradicate these organisms, and a summarization of the results of antigenic analysis of cultures obtained from all eighteen patients is also presented (table 1).

TABLE 1

Recapitulation of 18 cases suspected Paracolon bacillus infection

CLINICAL SYNDROME	SEVERITY	DURATION	ORGANISM	SHIGELLA ANTIGENS	SALMONELLA ANTIGENS	RESULT
		years				
1. Chronic enterocolitis*	Sev.	3	*Paracolon*	—	(*onderstepoort*) (I), (VI, XIV, XXV)	Cured
2. Pep. ulcer and chr. enterocolitis*	Sev.	4	*Paracolon*	—	Champaign XXXIX	Much impr.
3. Chronic colitis and malnutrition*	Mod.	7	*Paracolon*	Boyd 88, Sachs Q1167	—	Mod. impr.
4. Obsn. brucellosis; chr. colitis*	Sev.	3	*Paracolon*	—	C_2 *newport* VI, VIII	Cured
5. Chronic enterocolitis*	Mod.	10	*Paracolon*	Sachs Q-1030	—	Cured
6. Chronic enterocolitis	Mod. sev.	7	*Paracolon*	Boyd 288	—	—
7. Malnutrition and chronic colitis	Mod.	10	*Ps. aerugin*	Flexner W	—	—
8. Recurrent enterocolitis	Mild	7	*Paracolon*	Boyd group	—	—
9. Chronic colitis	Mild	4	*Paracolon*	—	—	—
10. Allergies and diarrheas	Mild	4	*Paracolon*	Flexner W., Boyd D19, P119, 103	C_1, *Cholerasuis* (VI, VII	—
11. Chronic enterocolitis	Mod.	4	*Paracolon*	—	—	—
12. Amebiasis (ameba not found)	Mod.	3	*Paracolon*	—	—	—
13. Functional spastic colon	Mild	4	*Proteus*	—	—	—
14. Pyelitis and enterocolitis	Mod.	2	*Paracolon*	—	—	—
15. Enterocolitis and hepatitis	Sev.	2	*Paracolon*	—	—	—
16. Chronic enterocolitis	Mod.	1	*Paracolon*	Boyd group	—	—
17. Recurrent enterocolitis	Mild	3	*Paracolon*	—	—	—
18. Chronic amebiasis (ameba found)	Sev.	3	*Paracolon and E. histolyt.*	Sachs Q-1167	C_2 *newport*, VI, VIII	

* Denotes streptomycin therapy completed.

Case 1. A 27-year old registered nurse dated the onset of persistent symptoms to the summer of 1942 when she was in New Orleans. She was studied at that time

for malaria but was finally diagnosed as acute gastroenteritis because of 6–8 bowel movements daily for 3 days, associated with tenderness and pains in the right lower quadrant. Intermittent milder attacks with some weakness and malaise recurred until June 1944 when she was again in New Orleans. She had a more severe attack then and was hospitalized three weeks with severe diarrhea, right-sided and central abdominal cramps, blood and mucus in the stools, and severe occipital headaches. She was observed for amebic dysentery and was given a course of emetine although no amebae were found. During this attack she had photophobia, mild neck rigidity, frequent vomiting, tenderness over the entire length of the colon, and subsequent muscle weakness for several weeks. There was an eosinophilia of 7%, and a food allergy was suspected but was not found after careful study. She was discharged as improved on 20 July 1944 with the diagnosis of "disease, undiagnosed, of alimentary tract, with vomiting". Subsequent lesser attacks followed, with cecal tenderness and diarrhea, and in 1945 the diarrhea alternated with periods of constipation, and increasing nervousness and emotional upsets developed. Following two courses of sulfa-therapy and one of penicillin for endocervicitis in 1945 she noticed temporary relief for about two weeks in her abdominal symptoms and headaches. Since April 1946 her abdominal and head symptoms have become more constant and she became nervous, irritable, emotionally unstable, tired and exhausted, and finally had to give up her work of professional nursing. Patient's admission complaints were frequent menstrual periods of several days duration, severe headaches and diarrhea accompanied by distress in the cecal area, nausea and vomiting, with often free blood in the stools. She had at times noticed easy bruising of her skin, and increasing frequency of bloody and sometimes tarry stools. Her blood count on 12 August 1946 revealed a color index of 1.08, WBC 5,200, platelets 196,000. The barium enema was negative, as was sigmoidoscopic examination. Rectal swab and repeated stool cultures revealed a paracolon bacillus containing the antigens of *Salmonella onderstepoort* VI, XIV, and XXV. An Army neuropsychiatrist who had at first suspected she was suffering from a purely functional (4) disorder, had later come to consider her condition to be on an organic basis, and when finally confronted with these bacteriological findings felt that a diagnosis of chronic Salmonellosis or bacillary dysentery was acceptable from the clinical standpoint.

The sensitivity of the organism to streptomycin was found to be approximately 4 units, and on 14 September 1946 the patient was started on a 12-day course of 2 grams orally and 2 grams parenterally in divided doses each day. She developed nearly all the streptomycin reactions quoted in the literature, many of which might be explainable on a basis of suddenly diminished renal function, since excretion of PSP dropped from 60 to 43 during the reaction period and then returned to normal after the drug was stopped, which was on the eighth day of administration. No record of blood-streptomycin levels could be obtained from the laboratory to which specimens were sent; however in view of the reaction it was presumed the levels were high. Immediately following treatment all her previous abdominal and head symptoms disappeared, and she shortly resumed her full time nursing work. Recheck stool studies in October and December 1946 showed no evidence of the para-

colon bacillus, and 5½ months after therapy she has had no recurrence of any of the symptoms which had plagued her almost continuously since 1942.

Case 2. A 24-year old white male veteran gave a history of indefinite onset of abdominal complaints in 1942, consisting of lower abdominal pains and discomfort associated with frequent looseness of the bowels. In October 1944 he was hospitalized for 3 days at the Carlsbad Army Air Base in New Mexico, for a moderately severe attack of diarrhea and cramps, with copious watery stools and some vomiting. In December 1944 he experienced a more severe attack at the same station and was hospitalized for two weeks, following admission with splitting headaches, fever, abdominal pains, severe diarrhea, and mild syncope. No commonly-recognized enteric pathogens were found, but he was given tablets which he thinks were "sulfa". He felt better for a time after discharge from the hospital but continued to have occasional attacks of diarrhea, abdominal pains, and associated headaches. In February 1946 he noticed a different type of pain, epigastric in location, with exacerbations in his diarrheas and vomiting. A milk diet reduced the frequency of the vomiting, but the diarrhea continued; he thought the Army food caused his troubles, so he suppressed his symptoms until after his separation in March 1946. However the diarrhea became worse after he went home, and civilian doctors were consulted, with little satisfaction to the patient. In June 1946, while employed as a civilian at an Army post, he continued to have anorexia, morning vomiting, and distressing diarrhea, and he was referred to the neuropsychiatrist as a functional case. After thorough neuropsychiatric study it was felt that there was an underlying organic basis for the patient's complaints. Further stool studies revealed a paracolon bacillus containing antigens of *Salmonella champaign* XXXIX, but no commonly-recognized enteric pathogens were detected. From July 20 to 24th the patient noticed increasing upper abdominal pain and passed several tarry stools, had considerable vomiting and generalized weakness. On July 24 he was admitted to a civilian hospital in syncope and was later transferred to a Miami Veteran's Hospital as a bleeding peptic ulcer case. On admission he was critically ill from loss of blood; three weeks later a G.I. series was performed and showed a markedly contracted and deformed duodenal cap, but no evidence of ulcer niche or crater. He responded well to conservative treatment and was discharged on 26 August 1946. Returning home, his diarrhea recurred and on 1 September he again had severe abdominal pains, and also pains and tenderness in the cecal area. Fearing a recurrence of his bleeding ulcer he contacted us and was admitted as a probable emergency. His severe symptoms shortly subsided except for diarrhea, cecal distress, extreme weakness and considerable anal pruritis. No blood was found in the stools but mucus and pus were present; he ran a low-grade afternoon temperature, and copious diarrhea continued, with lower abdominal distress predominant. Barium enema was negative but sigmoidoscopic examination revealed a diffuse inflammation with a mucopurulent exudate, and bleeding on slight pressure. The same strain of paracolon bacilli previously detected was cultured profusely from a sigmoid swab. Blood count showed 60% lymphocytes, 187,000 platelets, and a color index of 1.03; other-

wise the blood was normal. Neuropsychiatric study revealed irritability, mild belligerence, and dissatisfaction with everything. (It is of interest that this mental attitude (4) underwent a complete change during the latter part of streptomycin therapy, the man becoming cheerful, cooperative and optimistic; since then he has remained so.)

Streptomycin therapy was instituted on 16 September 1946 after ascertaining that the paracolon bacillus was inhibited by 5 units; four grams daily were given for 12 days, half orally and half parenterally. Treatment was uneventful except for band-like headaches coming on immediately after taking the *oral* doses only, and lasting about one-half hour. Some increase in the patient's lower abdominal distress and diarrhea occurred from the third to sixth day, and blood streptomycin levels varied from 2 to 8.5 units. Since this patient's discharge from hospital 5½ months ago he has felt much better and is working. He has had no recurrence of ulcer symptoms, but some intermittent looseness of the bowels persists. Re-check stool specimen in October 1946 showed that the previously-identified paracolon bacillus was not present although a paracolon without *Salmonella* or *Shigella* antigens was reported. Re-checks in November and December failed to show the presence of paracolons or other suspicious organisms.

Case 3. A 25-year old white male Army officer could not accurately date the onset of symptoms other than to say he had complained almost continuously of various gastrointestinal symptoms since 1939. He recalled that in 1938 he had suffered from frequent bronchitis, head and chest colds, and feelings of fullness in the lower chest. He became run-down thereafter, and in 1939 developed lassitude associated with upper abdominal distress, but studies made at Johns Hopkins hospital revealed nothing more than moderate physical and mental exhaustion, without apparent cause. He thereafter forced himself to work, and deliberately minimized his symptoms. In 1942 his bowels became generally loose, with 3–4 movements daily, mostly in the mornings, and associated with gas and anorexia. The abdominal distress settled in the lower left quadrant and seemed worse after meals. He was hospitalized at Scott Field, Illinois, in January 1943 for these symptoms and for irregular heart and inconstant murmurs, and ultimately was diagnosed as spastic colitis, probably functional. He felt better during a period of 6 months of a more physically-active life up until April 1944, but upon returning to sedentary work the diarrheas returned, left lower quadrant distress increased, and morning tiredness became prevalent. During one year's service in Trinidad up to April 1946 he developed chronic anorexia, his bowels became alternately loose and constipated, and he became nervous and irritable. In the spring of 1946 he began to notice blackish and greenish-black stools, sometimes tinged with free blood; and he also noted feelings of feverishness, and of dizziness upon changing posture. He returned to the United States on a duty status in April 1946 and soon thereafter was seen as an out-patient, being treated as a functional case for several months. The abdominal discomfort was generalized, but worse in the left lower quadrant, and there was no relationship between his symptoms and periods of mental or physical stress. The

neuropsychiatrist concluded that these symptoms were on an organic basis, and later stool studies revealed a paracolon bacillus having *Shigella* antigens of Boyd 88 and Sachs Q-1167 strains, but no commonly-recognized pathogens. Pus was present in the stools, and a blood study showed 14,750 WBC, blood platelets 256,000, and sedimentation rate 27 mm. per hour; the blood was normal otherwise. Barium enema on 26 August showed a high splenic flexure and poor visualization of the descending colon. Sigmoidoscopic examination revealed a congested anterior wall of the rectosigmoid with confluent small reddened areas on a dull-looking mucosa, reported as: "painless area of rectal irritation, evidently a chronic low-grade infection with friable mucosa". Sigmoid swab showed innumerable RBC and a positive culture for the paracolon bacillus.

On "functional" placebos (4) the patient continued to feel worse and to lose weight. The streptomycin sensitivity of his paracolon bacillus was found to be 12 to 15 units, and more sensitive than *E. coli* "W" or *E. typhosa;* therefore the patient was given a 12-day course of the drug commencing 23 September 1946. During treatment he developed no untoward reactions except some increase in symptoms between the third and sixth days. Blood streptomycin levels varied from 2.5 to 6.0 units. One month after treatment he reported little improvement in his general condition; however he had gained weight and looked better, and recheck stool cultures showed no evidence of the paracolon containing *Shigella* antigens although a paracolon organism was present. It was felt that this may have been a "loss variant" (1, 7, 8, 9) of the former organism; therefore he was given a 3 day course of combined streptomycin, penicillin, and sulfadiazine commencing 29 November 1946, with the idea of simultaneously attacking the paracolon bacillus and possible secondary invaders. Subsequent stool cultures in December 1946 and January 1947 were entirely negative, and there has been a cessation of the patient's abdominal complaints associated with a further improvement in his general condition. Although it is not possible as yet to give a final evaluation in this case, the patient's well-being and general appearance $3\frac{1}{2}$ months after the second course of treatment have improved substantially, as contrasted with his progressively down-hill course prior to institution of therapy in September.

Case 4. A 30-year old housewife was admitted complaining of fatigability, nausea, vomiting, back pain, fever, chills, and some diarrhea. She appeared chronically ill and at one time had been suspected of having tuberculosis. She gave a history of appendectomy in 1936. In February 1945 she began to notice weakness, pains in her knees and elbows, chills and fever. Following positive skin tests at that time for brucellosis she recalled that in December 1944 she had used a pound of raw butter obtained from a farm near Dayton, Ohio. Thereupon she was treated with heavy doses of *Brucella* vaccine for 4 months, although no positive blood cultures were obtained. She experienced severe chills and fevers after each dose of vaccine and stated that she felt somewhat better after the course, but not as well as before the onset of her illness. Her menses became irregular, and in March 1946 multiple ovarian cysts were found and excised, and a uterine suspension was performed.

Later she noticed increased fatigue and afternoon temperatures, lower abdominal discomfort chiefly on the left side, and had an attack of urinary frequency and burning for which she was given a short course of penicillin, with temporary improvement in most of her symptoms. Subsequently her back pain began as sharp shooting pains just below the costal margins on both sides. For a week before admission she had increased back pain, nausea, frequent vomiting, and abdominal discomfort. Substernal burning was present on eating acid or spicy foods, and she had avoided fatty foods for some time. She had become quite tired and exhausted, was unable to do her housework, and reported losing weight for the preceding month, with frequent headaches. A presumptive diagnosis of chronic brucellosis was made, and on 16 September 1946 her blood titer for *Brucella melitensis* was found to be 1/1280, and for *Brucella abortus* 1/160. Spine X-rays were negative, as was the urine. Afternoon temperatures persisted, and the blood sedimentation rate was 25 mm, with the blood picture essentially normal except for 11,450 WBC and 2% eosinophiles. Blood culture for *Brucella* was negative. In view of the diarrhea, stool cultures were performed, and an organism was isolated which was at first stated to be either a new strain of *Salmonella*, or else a paracolon bacillus having *Salmonella newport* somatic (VI–VIII) antigens. It was later determined that the organism was a paracolon containing the aforementioned antigens. Barium enema and sigmoidoscopic examination were essentially negative, although the cecum filled incompletely and the transverse colon was ptotic. Sulfadiazine was given for 4 days with no apparent effect upon her temperature or symptoms. Some vaginal bleeding noted was felt to represent ovarian failure or to be due to the debility of brucellosis. However, many of her symptoms were considered atypical for brucellosis, and appeared to be more compatible with chronic dysentery. Therefore, after determining that the paracolon bacillus was inhibited by 10 units of streptomycin, she was given a 12-day course, commencing on 12 October 1946. Her symptoms, particularly the diarrhea, increased for a few days and then subsided, and she felt much improved by the 9th day. Reported blood streptomycin levels varied from 4.5 to 28 units. Upon her discharge she stated that she felt better than she had for several years, except for some dizziness, and had gained several pounds in weight. Unfortunately the vertigo which commenced to develop under streptomycin therapy increased for some weeks after cessation of therapy, becoming so severe that she at times required assistance in walking. In spite of this distressing condition she maintained that she preferred to feel that way than the way she had felt prior to therapy. Two months after treatment her vertigo commenced to subside, and is continuing to improve four months after onset. Stool cultures in late October and December 1946 revealed no evidence of the paracolon bacillus or other suspicious organisms. She has had no recurrence of any of her original symptoms five months after therapy, and has resumed her normal housework.

DISCUSSION

It seems reasonable to assume that an enteric organism found in a case of clinical dysentery or enterocolitis, which contains the antigens and/or im-

munogens of one or more of the commonly-recognized pathogens, is the organism responsible for symptoms, disordered physiology, and pathology if any. Sieve (12) believes that chronic infection with its usual toxemia interferes with the orderly mechanism attending the important roles of hormones and vitamins, thus upsetting physiological balance and creating physiological or functional disorders. He emphasizes that in some nutritional disorders the true damaging agents are the toxins of pathogenic bacteria which produce a systemic toxemia. This toxemia interferes with or inhibits vitamin absorption and synthesis, and therefore nutritional deficiencies result. Luippold (8–9) observes that new types of *Salmonellae* are almost daily being indicted as infectious agents of gastrointestinal disease chiefly on the basis of their antigenic relationship to members of the *Salmonella* group. No one questions their pathogenicity, therefore the same criterion could be a valid one in judging the pathogenicity of paracolons many of which are intimately related antigenically to the *Salmonellae* and *Shigellae*.

In at least one specific instance (that of Case 5 in table 1, to be further reported in a separate paper) an exhaustive study was made of the paracolon bacillus isolated (9) and it was concluded by recognized authority that the etiological agent of the patient's enterocolitis was the paracolon in question. This organism was unique in that it contained *all* the antigens of a *Shigella* strain; a corollary to this situation might be cited in the recent report by Seligmann and Saphra (11) on a coliform having *all* the antigens of a *Salmonella* strain.

There are many complexities involved in making a final identification of enteric bacteria. For example, under presently-accepted definitions of the Genus *Salmonella*, organisms suspected of being *Salmonellae* can neither be included nor excluded from the genus solely on the basis of certain biochemical reactions; antigenic analysis must be the final criterion for proving unknowns. Yet, a sketchy analysis may well result in premature and erroneous identification of paracolons as *Salmonellae* by reputable laboratories, as was the case at a Southern Army Camp a few years ago where an outbreak of acute gastroenteritis was at first reported to be paratyphoid A fever, but was later shown to be caused by a paracolon bacillus having the major somatic antigens of *S. paratyphi* A.

In each of the four cases reported in detail here, and also in the remainder of the 18 patients studied (table 1) the histories and clinical findings were suggestive of a chronic infectious process, in that low-grade fever, general malaise, debilitation, headaches, and reduced functional capacity were present. The sequence of symptoms suggests that as time went on, other bodily systems besides the gastrointestinal tract became affected, such as the neurological, cardiovascular, and hematopoietic systems. While it may be asserted that the

therapeutic tests applied to these cases by means of streptomycin could have given the same results by eliminating an undetected focus of infection by organisms other than the paracolon bacilli, the fact remains that the paracolon bacilli were the only suspicious organisms isolated, and cure or improvement in gastrointestinal and other symptoms of long standing was concurrent with the permanent disappearance of these organisms from the patient's stools. Significantly in this connection, the patient suspected of having chronic brucellosis (Case 4) remains cured five months after a relatively short course of streptomycin therapy. Since streptomycin therapy is being reported as unsuccessful in brucellosis, it may be inferred that this patient did not have that disease and that her syndrome was that of a paracolon bacillus infection.

It will be observed that after streptomycin therapy 3 out of five cases receiving such therapy were reported as cured, one case much improved, and one case only moderately improved. In the latter (Case 3) the records of blood streptomycin levels during the first course of treatment showed only a maximum of 6 "S" units whereas in two of the apparently cured cases the maximum levels reached from 9 to 28 units. Case 3 also had shown the highest streptomycin resistance in preliminary sensitivity tests of the organism.

In the investigation reported here, it is of interest that in detecting these suspicious organisms in the primary stool cultures no difficult or special techniques were necessary; all that was needed was curiosity and the urge to further investigate those organisms which grew as relatively colorless colonies on SS agar, or which grew on SS agar after primary isolation in selenite broth. Various routines used seemed to achieve fairly uniform results in primary isolation, the simplest one consisting of streaking $\frac{1}{2}$ of an SS agar plate with a loop which had been dipped in raw feces, and streaking the other half of the same plate with a loop-full of a saline suspension of $\frac{1}{2}$ gram feces in 3 to 5 cc. sterile saline. Selected colorless or otherwise suspicious colonies appearing on SS agar after 24 hours incubation were then streaked and stabbed into Kligler slants and observed up to 72 hours. The Kligler tubes which developed an acid butt with alkaline slant, with or without gas or H_2S production, were in most instances found to be paracolon bacilli.

Antigenic analysis performed by the Division of Typhoid Research, Army Medical School, revealed the interesting fact that of 16 paracolon cultures examined, 11 contained *Salmonella* or *Shigella* antigens and two of them contained both types. In the 8 paracolon strains containing *Shigella* antigens the following antigens were identified, several different antigens often occurring in the same strain:

Flexner W
Boyd 88, 103, 288, D-19, and P-119
Sachs Q-1030 and Q-1167

Similarly, in the 5 cultures containing *Salmonella* antigens the strains represented were:

Salmonella group	*Antigen*	*Cases*
Group C_2 (newport)	VI, VIII	2
Group C_1 (cholera-suis)	VI, VII	1
S. onderstepoort	VI, XIV, XXV	1
S. champaign	XXXIX	1

The recapitulation of all 18 cases presented in Table I, shows the clinical diagnoses in relation to the organisms and antigens later found, and the duration and relative severity of symptoms in each case. The asterisks denote the 5 cases in which streptomycin therapy was completed. It will be noted that one culture submitted as a suspected paracolon bacillus turned out to be *Pseudomonas aeruginosa* containing a very heavy component of Flexner W *Shigella* antigens; one other culture turned out to be a proteus with neither *Salmonella* nor *Shigella* antigens. (Neter and Clark (10) reported a high percentage of *B. morganii* type I organisms in a large series of stool cultures from children ill with diarrheal diseases, which suggests that these organisms were in fact pathogenic for the individual cases from whom they were isolated. Antigenic analysis of those particular cultures might have given very interesting results).

SUMMARY

1. Four case reports are presented in which syndromes of chronic dysentery are closely associated with the finding of paracolon bacilli in the patient's stools.

2. Streptomycin therapy in these four cases and in one additional case to be reported separately resulted in eliminating the suspected paracolon bacilli, and in clinical cure or improvement in the patients.

3. Eleven additional patients having somewhat similar histories, clinical manifestations, and laboratory findings, were found to be harboring paracolon bacilli.

4. Antigenic analysis of 16 different paracolon organisms which were isolated from this series of cases revealed the presence of *Salmonella* or *Shigella* antigens in nearly 70%.

5. In one additional case having similar clinical manifestations a *Pseudomonas aeruginosa* organism was found which contained a heavy concentration of antigens of the Flexner W strain of *Shigellae*.

6. A possible relationship between paracolon infections and obscure chronic diseases has been mentioned.

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GASTRIC SURGERY: A REVIEW OF THE LITERATURE FOR 1946

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During the past year the effect of vagus resection in the control of peptic ulcer has continued to evoke interest. Although in general the reports have been favorable, attention has been called to untoward side effects that later may change opinion considerably regarding the value of this new therapeutic method. Perhaps of more value than the interest in vagus resection itself is the resultant stimulation of renewed interest in physiology as it applies to gastric secretion and to neurogenic influence on the stomach and expecially the application of these physiologic studies to practical use in the understanding and treatment of the ulcer problem. Some of these studies may have a direct bearing upon this problem and we believe any progress in treatment of ulcer must be in this direction rather than in more emphasis on surgical methods.

PHYSIOLOGY

Brummer (1) devised a new method for the determination of the mucin content of gastric juice, which he tried on 50 healthy subjects and 95 with various gastric disorders. The average mucin content was 0.5 per cent, and was slightly higher after a test meal than in the fasting stomach. Histamine and insulin had no effect on the mucin content, and no clear difference was found in persons with duodenal ulcer or gastritis.

Price and Lee (2) found that all living tissues implanted in the stomach, except gastric epithelium, underwent digestion. Their microscopic studies suggest that a surface of active fibrosis offers resistance to digestion and that even more opposition is offered by a layer of granulation tissue. Such tissue responses serve as protective mechanisms. Once these tissues are covered with proliferating gastric epithelium they appear to be safe from further corrosive action by normal gastric juice.

Sandweiss et al. (3, 4) pointed out that the volume and total acidity of nocturnal gastric secretion is the same in patients with duodenal ulcer as in normal subjects when determined by continuous suction. They concluded that the greater quantity of gastric juice obtained when intermittent single aspirations are made from patients with duodenal ulcer is not owing to hypersecretion, but to a state of delayed gastric emptying. The need for additional studies is

therefore apparent. This may alter the conception of vagal influence on night secretion.

Further studies have been carried out on the effects of various agents on gastric secretion. Glenn (5) found that histamine is the maximum stimulant for attainable acid, regardless of the presence of ulcer; however, a greater volume of gastric juice is produced in cases of peptic ulcer. Sangster et al. (6) showed that benadryl had no depressant effect on gastric acidity when administered to dogs with gastric pouches.

Diaz-Rubio (7) reported that an intravenous injection of nicotinic acid produces an increase of free acidity in normal subjects and in those with achylia, but not in the achlorhydria of pellagra. Hartiala (8) studied the influence of anoxia on gastric acid secretion: in the low pressure chamber, high altitude (over 13,000 feet) decreased hydrochloric acid secretion owing to the anoxia and not to the alkalosis.

DIAGNOSIS

Roentgen-Ray. In an excellent summary of the differential diagnosis of juxtapyloric ulcer and cancer, Hellmer (9) emphasized that many roentgen examinations often are necessary since the size of the niche is not a valid basis for distinction. Unless the clinician is to operate on all patients with gastric ulcers, a trial of medical therapy is indicated with subsequent roentgenologic follow-up. Since shrinkage of the ulcer crater does not rule out cancer, the author concluded that the roentgenologic diagnosis of benign gastric ulcer requires complete disappearance of the niche, with nothing remaining at the site to suggest carcinomatous infiltration. We agree with this but believe that we should go further—that all patients with gastric ulcer should be operated on earlier, with especial stress on the prepyloric and greater curvature ulcers. Paulino (10) urged that the roentgenologist should not attempt to diagnose operability of malignant gastric ulcers, although ulcers with a diameter greater than 2.5 cm., those with irregular contours, prepyloric and greater curvature ulcers should be considered malignant until proven otherwise. In our own experience 23 per cent of benign gastric ulcers were larger than 2.5 cm.

Of 384 patients with benign gastric ulcer, 41 per cent had niches more than 1.5 cm. and 6.5 per cent had niches more than 3 cm. in diameter (11).

Schilling (12) reported the case of a man in whom, during fluoroscopy, barium was observed to streak out of the duodenal cap and promptly outline the right lower boundary of the peritoneal cavity. A perforation of the anterior wall, 1.5 cm. in diameter, was found at operation; the patient did well following closure.

Barium sulfate was instilled into the peritoneal cavities of 3 dogs and found to produce dense fibrous adhesions. It is well known that a barium meal

should be given with caution to a patient suffering with an acute exacerbation of ulcer distress because acute perforation may occur during or after such examination.

Gastroscopy. Further studies appeared during the year comparing the relative merits of the gastroscope and roentgen-rays in diagnosis. Ricketts and Pollard (13) published an analysis of 1297 patients with gastric disease studied by both roentgenograms and gastroscopy. They reported positive roentgenograms with negative gastroscopic findings in 46, and negative roentgenograms with positive gastroscopic findings in 309 of 355 cases; most of these, however, were cases of chronic gastritis. In general, while the shape, contour, motor function and gross lesions are seen better with roentgenograms, mucosal and small lesions are seen better with the gastroscope. Benedict (14) correlated the gastroscopic, roentgenologic and pathologic findings in 245 proved cases of stomach disease and concluded that both methods of diagnosis are valuable. Gastroscopy furnishes more information when the lesion can be visualized, but further technical improvement is desirable to eliminate the blind spots.

Freeman (15) performed gastroscopy on 50 patients with duodenal ulcer, and noted that in 38 (76 per cent) the mucosa was hyperplastic. He stated that this type of mucosa secretes more fluid, and is more likely to produce stomal ulceration after gastroenterostomy. Gastroscopy of patients before and after Somervell's operation (arterial ligation) revealed a disappearance of the hyperplasia with return to normal appearance of the mucosa.

Hyperplasia of gastric mucosa is very commonly seen at the operating table in duodenal ulcers, especially in long-standing ulcers with varying degrees of obstruction.

Paul and Antes (16) reported a perforation of the esophagus caused by the flexible gastroscope, treated without fatality; they had previously reported a similar case with death in twenty-four hours. These 2 cases occurred in over 1850 gastroscopies. This accident occurs occasionally with esophagoscopy and great care should be used in these types of endoscopic examination to prevent such a serious complication. Robinson (17) reported that 10 cc. of fluorescein in the stomach aids in outlining and demonstrating an ulcer, and thus makes possible a more accurate estimation of the diameter.

PEPTIC ULCER

Incidence and statistics. Linn (18) reported an analysis of peptic ulcer in South Australia based on a study of 1027 hospital cases. The over-all mortality rate was 8 per cent, half of which was owing to perforations. Perforated gastric ulcer was twice as common as duodenal ulcer, the reverse of elsewhere. Fifty per cent of the patients used alcohol, and 80 per cent tobacco. Of the

patients treated with gastroenterostomy stomal ulcer developed in 30.6 per cent.

Gastric ulcer is much less common than duodenal ulcer, 1 to 10, and perforation of gastric ulcer, therefore, is fairly uncommon in the states; the percentage frequency of perforation is not as high as that in duodenal ulcer.

Etiology and pathogenesis. Kristenson (19) made injection preparations to show that the circulation to the pyloric antrum and first portion of the duodenum is much less than to the rest of the stomach and small intestine. This poor circulation is further embarrassed in the upright position, and it is suggested that ulcer might be a result of the upright position of the human race. Rest in the horizontal position after meals is advised for therapy. Rest in bed for the ulcer patient during treatment is a valuable addition to the ulcer regimen but whether there is an explanation is doubtful; it is at least interesting.

Jamieson et al. (20) questioned 473 patients who had had an acute perforation and found no evidence that increases or decreases in tobacco consumption influenced the severity of symptoms. Certainly patients do better on ulcer therapy if smoking is prohibited and the bad effects of smoking upon ulcer distress is well recognized.

After a review of opinions on why the stomach resists digestion by its own ferments, Bachrach, Grossman and Ivy (21) reaffirmed the theory that the farther away the mucosa is from the source of acid formation, the less the resistance of surface epithelium to injury by acid. Most ulcer craters disappear within six weeks of medical therapy. The ulcer patient can be described as one with either a normally resistant mucosa subject to abnormally high gastric secretions, or a less resistant mucosa susceptible to injury at normal acid and pepsin levels. The therapeutic aim, therefore, is to find a method to reduce secretion or to improve cell resistance.

The occurrence of Curling's ulcer with tumor has been well recognized. Hartman (22) produced third degree burns of 50 per cent of the body surface of dogs; all showed positive blood cultures and 77.7 per cent had acute duodenal ulcers. Penicillin reduced the incidence of ulcer to 23 per cent. Therefore, local and resulting systemic infection are of major etiologic importance in the pathogenesis of Curling's ulcer. Congestion and edema of the duodenal and gastric mucosa are precursors of ulceration and result from shock. Such a basis for the ulcer is logical and founded on keen observation.

Medical treatment. In a summary of the present status of the problem of peptic ulcer, Ivy (23) emphasized that in 10 per cent of the population the disease will develop during their lifetime. Only one type of ulcer occurring in man has been produced experimentally, and that is the postoperative jejunal ulcer. The main problem in peptic ulcer therapy is to prevent recurrences. Surgical methods are stopgaps until a more effective medical method is dis-

covered. Eight of 32 patients receiving enterogastrone injections three times a week had recurrences; 22 of 26 patients receiving it six times a week remained asymptomatic, and of 10 patients receiving it for one year, none had had symptoms one to twenty-eight months after stopping treatment. Ivy and his group are now working with an oral preparation but have no results to report as yet. Such an approach to the treatment of peptic ulcer is a long wished for panacea; it is much more logical than nerve division, and so forth, and offers a more fruitful source of solution of this problem. It will take much more work and investigation before its value can be determined.

In another report from Ivy's (24) clinic a method is described of a preparation of enterogastrone concentrate of uniform potency suitable for parenteral injection in human beings. A therapeutic trial on 43 Mann-Williamson dogs and on 58 patients with proved peptic ulcer has demonstrated that the material is probably effective in preventing recurrences during the period of its administration and for an undetermined length of time afterwards. The protection afforded cannot be explained by inhibition of gastric secretion.

On the other hand, Hubacher (25) reported on enterogastrone prepared in Switzerland from the stomach and small intestine of animals. In 54 cases, 44 good results were obtained without dietary or other treatment. With regard to physiology, it was found that enterogastrone diminishes gastric secretion, decreases gastric motility, and participates in the regulation of the blood supply to the gastric and duodenal mucosa.

Following the treatment recommended by Co Tui, Ruggiero (26) administered protein hydrolysates (0.6 gm. of nitrogen per kilogram of body weight) and dextrimaltose number 2 (40 to 50 calories per kilogram) to 134 ambulatory patients with peptic ulcer. There were 16 failures; 118 patients had no further symptoms. Vinci et al. (27) reported that a high protein, high caloric diet favorably influences tissue repair and the healing of medically amenable ulcers. Nine of 30 hospitalized patients, however, required surgery.

Friedlaender (28) treated 5 patients with peptic ulcer with injections of female sex hormone, and claimed a reduction in pain with less necessity for a strict diet. Side effects were noted, however; perhaps the effect is more psychic than clinical, as is true so often with injection therapy.

Yasinovskiy (29) treated patients with peptic ulcer with insulin and the usual diet plus sugar. Since the improvement in symptoms was associated with an increase in gastric acidity, the author believes the effect of insulin on a functionally inadequate liver and pancreas is responsible for the good results obtained. This is difficult to evaluate since insulin, by creating hypoglycemia, increases acid gastric secretion and is one of the tests used to estimate the completeness of vagal resection.

Cummins et al. (30) emphasized that a determination of "healing time" is

important to evaluate new methods of treatment and to judge the efficacy of treatment in a given case. The average healing time was found by the roentgenogram to be thirty-seven days for duodenal ulcer and forty-two days for gastric ulcer with the usual therapy. No correlation could be found between the healing time and the size of the crater, age of the patient, or duration of symptoms. Peptic ulcer is characterized by a striking tendency to recur after it has healed. It should be pointed out that peptic ulcer also shows a remarkable tendency to heal when a simple medical regimen is carefully followed.

Krarup (31) summarized the results of medical treatment of 665 cases of uncomplicated peptic ulcer. The immediate results of treatment were good. After five years, 29 per cent had recovered, 36 per cent were improved, and 35 per cent had a poor result. Age and sex had little bearing on the outcome. The longer the duration of symptoms, however, the less chance there was for recovery. Fifty-eight patients had surgical intervention, 17 for perforation and 41 for pain. Relapses were frequent (86 per cent in gastric ulcer), and the author concluded that since medical treatment had effected such poor results, the indications for resection should be broadened.

Indications for surgery. Hinton (32) summarized the indications for operation in the treatment of peptic ulcers. He took the position that operation should be advised in all cases of gastric ulcer which do not respond quickly to treatment. In this we agree, and certainly all patients with long-standing gastric ulcers should be operated on at once without medical treatment. The location of the gastric ulcer is also important. Only patients with intractable duodenal ulcers should be operated on, and massive hemorrhage in general should be treated conservatively.

Complications. Perforation. Olson and Norgore (33) reviewed 166 cases of perforated peptic ulcer at the King County Hospital in Seattle. They found obliteration of liver dulness a valuable physical sign if the patient is placed on his left side for five minutes, and stated that roentgenograms for pneumoperitoneum are better if the patient is placed on his left side for twenty minutes, rather than upright. Operation was done in 138 cases, with 14 wound dehiscences and 24 wound infections. A 3-inch transverse incision was used and the perforation closed with omentum; sulfonamides intraperitoneally or drains were not employed and the incision was usually closed with cotton or wire. The over-all mortality was 27.7 per cent, most of the deaths being the result of peritonitis or pulmonary complications. Mortality can be kept at a minimum by the simplest type of operation.

Graham (34) reported a series of 125 consecutive operations in Toronto with 8 deaths, a mortality of 6.4 per cent. He emphasized that the serious clinical state following perforation is not the result of peritoneal infection but of

nutritional and biochemical imbalance with shock, and stressed the importance of preoperative and postoperative care. Since this is an emergency operation, the simplest effective procedure is indicated. Drainage of the abdomen is unnecessary and the intraperitoneal use of sulfanilamide is superfluous. Resection in the presence of intra-abdominal infection is a serious affair and will undoubtedly increase the mortality if routinely employed. Simple closure only is to be recommended.

Forty (35) reported a series of 100 closures with 17 deaths. There were 88 men and 12 women treated by closure of the perforation with a single catgut stitch reinforced with three silk inversion sutures and patched with omentum. The abdomen was drained in 54 cases. Of 70 cases followed, recurrent symptoms developed in 38 within a year, and 10 patients required further operation.

McCarthy and Knoepp (36) reported on 28 cases in which operation was performed, with only 1 death, a mortality of 3.6 per cent. Most of these patients were vigorous young men treated at an army station hospital.

Two reports appeared in the Scandinavian literature advocating more than just simple closure for perforated ulcers. Sandberg (37) recommended excision of the ulcer with closure by sutures and an omental flap, mopping of the abdomen, and gastrostomy. Resection is justifiable in certain cases, such as a young patient with obstruction. No statistics were presented. Saxholm (38) operated on 76 patients with an average age of 43 years, and stated that resection is well borne and gives better results than other operations. He performed subtotal gastrectomy in 64 patients, simple closure in 11, and closure plus gastroenterostomy in 1, with a total of 10 deaths. The mortality after resection for acute perforation was 6.2 per cent, as compared to a rate of 4.7 per cent for gastric resection for uncomplicated ulcer during the same period. Late results in 49 patients showed 27 well, 21 improved, and 1 not improved.

In reporting the results of immediate operation for perforated ulcer, Baritell (39) commented that 5 patients, who appeared to have improved when first seen twelve hours or more after probable perforation, were not operated on, the stomachs were aspirated, and all recovered. A young man who refused operation or other treatment died. Only 1 of 88 patients treated surgically died; this is the lowest mortality rate (1.1 per cent) recorded up to the present time.

Two reports appeared in the British literature on the nonoperative treatment of perforated ulcer. Taylor (40) performed gastric aspiration without operation in 28 cases, 26 with duodenal and 2 with gastric perforations; 4 patients died. He believes that if the stomach is kept empty, the defect will seal itself off and operation will accomplish nothing. Operation is indicated, however, if the stomach is full from a recent meal or pyloric obstruction, or if there is evidence of spreading peritonitis. Certainly it is a valuable method of

treatment when the patient is in poor condition and with spreading peritonitis and should be considered more often in these cases if the diagnosis can be established.

Illingworth et al. (41) published a follow-up survey of 880 patients operated upon with simple closure of a perforation. The mortality rate was 17 per cent. Ninety-five per cent of the patients were male, and 87 per cent of the ulcers were duodenal. At the end of the first year 60 per cent of the patients were symptom free, 20 per cent had mild symptoms, and 20 per cent had a severe relapse. By the end of the fifth year 30 per cent were symptom free, 20 per cent had mild symptoms, and 50 per cent had a severe relapse. In a similar study, Houston (42) analyzed the results of simple suture of a perforated peptic ulcer in 538 cases. Thirty-five per cent had had no further symptoms for an indefinite period. One-third of those having further symptoms required subsequent operation. Most of the recurrences were noted within two years, the longest interval being five years.

It is well known that perforation of an ulcer *per se* does not effect a cure of the ulcer. Such ulcers have the same opportunity to respond or fail under good medical treatment and the indications for surgical intervention after treatment remain the same.

Hemorrhage. Eads (43) presented a statistical analysis of 129 patients with massive gastrointestinal hemorrhage, of whom only 3 were women. In 23 per cent these were initial hemorrhages and the others were recurrent. Peptic ulcer accounted for 80.6 per cent of the cases (duodenal 72.8 per cent, gastric 6.2 per cent, and jejunal 1.6 per cent). Esophageal varices were found in 6.2 per cent of the total, and gastric carcinoma in 1.6 per cent. There were 3 deaths, 2 from large prepyloric ulcers and 1 from esophageal varices. The mortality rate was 2.3 per cent with medical treatment.

Zinninger (44) stated that the other conditions which may simulate bleeding ulcer are esophageal varices secondary to hepatic cirrhosis or portal hypertension, diffuse gastritis, bleeding tumor, hemorrhagic disease, and aneurysm with erosion into the esophagus or duodenum. If the bleeding is massive, continuous or recurrent, and particularly if the patient is past 60 years, operation should be performed after adequate blood replacement. The progress of bleeding may be estimated by frequent blood pressure, red cell count, hemoglobin and hematocrit determinations. We believe erythrocyte counts and hemoglobin determinations are of little value in determining blood loss due to changes in blood volume. Rising pulse rate and decreasing blood pressure indicates a continuance of blood loss which should be heeded more than blood counts.

The type of operative procedure must be selected for each case. Excision of the ulcer with partial gastrectomy is the method of choice, but the condi-

tion of the patient may not permit such an extensive procedure. Ligation of the vessels from outside the stomach may control bleeding from a gastric ulcer but a duodenal ulcer will require duodenotomy with a transfixion suture of the ulcer bed around the bleeding site, followed by closure of the duodenum or resection.

Bohmansson (45) presented his observations on over 200 patients with massive hemorrhage caused by ulcer who were submitted to operation during the acute stage of the hemorrhage. Although it is admitted that the Meulengracht method has value, there are certain cases in which radical surgery offers the only hope of survival. Operation should be undertaken as soon as shock is treated, to avoid danger of another hemorrhage. Bohmansson uses a Billroth I or II resection under spinal anesthesia, and stresses the need for close cooperation between the internist and surgeon in deciding the course of treatment. In this series 7 per cent of the total number of patients with bleeding ulcer were operated on, with a postoperative mortality of 5.2 per cent. The mortality for conservative medical treatment was 5 per cent.

Gordon-Taylor (46) discussed the present position of surgery in the treatment of bleeding peptic ulcer and analyzed the results of therapy in over 1700 cases. The mortality was 10 per cent as compared to a rate of 24 per cent during the previous decade. Operation is indicated also when there is evidence of obstruction, in patients past 50, and when the patient has been under adequate medical treatment. He stated that partial gastrectomy is the operation of choice.

A series of 337 patients with massive hemorrhage from ulcer is analyzed by Heuer (47). Eighteen deaths occurred under medical treatment, and 9 of the 31 patients operated upon died. The fatal type of hemorrhage was usually due to a duodenal ulcer located on the posterior wall or a gastric ulcer on the lesser curvature. We believe most massive bleeding occurs from ulcers in these areas. The indications for surgery are failure to improve promptly under strict medical treatment and recurrence of hemorrhage while under treatment. Local ligation of the vessels is unsatisfactory, and local excision of the bleeding ulcer and gastric resection are the best procedures.

Wilkinson and Tracey (48) analyzed a series of 140 cases of peptic ulcer with hemorrhage as the presenting symptom. Of this group, 125 were males. There were 5 deaths (3.5 per cent). Of the 70 patients with first hemorrhage there was only 1 death (1.4 per cent). Operation was performed in 61 per cent of the patients with recurrent hemorrhages, and one-third of these had recurrent hemorrhage after the surgical procedure. This may be compared to 23 per cent with satisfactory results from medical treatment.

Marshall and Nicholson (49) reported a case of massive hemorrhage in which operation was performed while the patient was in a critical condition. Cyclo-

propane anesthesia was used with curare, and 3500 cc. of blood was administered in the operating room. In this case the duodenum was opened and the gastroduodenal artery transfixed with silk mattress sutures, since the patient was in no condition for resection; gastroenterostomy was performed for obstruction. The authors stated that operation should be performed only in cases of massive hemorrhage uncontrolled by conservative measures. The fatalities occur most frequently in older patients with arteriosclerosis or a long-standing chronic ulcer accompanied by much fibrosis.

Surgical treatment. Subtotal gastrectomy. Allen and Welch (50) presented a critical analysis of subtotal gastrectomy for duodenal ulcer performed on 195 patients, with follow-up studies in 136 cases. The three main indications for operation were cicatricial stenosis, massive hemorrhage and intractable pain. It is estimated that from 10 per cent to 15 per cent of all patients with duodenal ulcers must be treated surgically. Persistent symptoms of some degree occurred in about a third of the cases. In our experience 7 per cent of patients with duodenal ulcer required surgical intervention. A posterior short loop anastomosis is preferred to the antecolic type, since it is claimed that each additional few centimeters of small intestine proximal to the anastomosis add to the incidence of marginal ulcer. There were 3 jejunal ulcers in the follow-up group. The surgical mortality was 4.5 per cent, and 87 per cent of the patients remained well after resection. In 700 consecutive resections for ulcer, we have seen no difficulty following antecolic anastomosis and believe the scope of resection has more to do with recurrence than the length of the jejunal loop.

King (51) reviewed 75 cases of subtotal gastrectomy for ulcer, with no deaths. He uses the Hofmeister technic, and described the details of his preoperative and postoperative care.

Colp and Druckerman (52) stated that in selected cases of high-lying chronic gastric ulcers, palliative gastrectomy produces permanent gastric achlorhydria with subsequent healing and disappearance of the ulcer which was left *in situ*. The patients have remained free of symptoms with no recurrence of gastric or jejunal ulcer. This operation is indicated in benign ulcers of the upper third of the stomach. In 8 cases there was 1 death (from coronary thrombosis). This is a valuable method for high-lying ulcers but with cleansing of tissue of the lesser curvature, many of these ulcers can be removed.

Vagotomy. Following extensive studies of the effect of vagotomy on gastric secretion and motility in patients with peptic ulcer, Dragstedt et al. (53, 54) published the following conclusions:

1. Continuous night secretion of gastric juice in the empty stomach of patients with peptic ulcer is usually much greater than in normal individuals.

2. This hypersecretion is chiefly of neurogenic origin and is much reduced by vagotomy.

3. The empty stomach of ulcer patients often displays hypertonicity and hypermotility with exaggerated hunger contractions, and these are returned to a normal state after vagotomy.

4. Complete section of the vagus nerves to the stomach abolishes the secretion of gastric juice produced by a sham meal or by insulin hypoglycemia, but has little or no effect on the response to histamine or caffeine.

Baronofsky et al. (55) found that vagotomy fails to protect the experimental animal against histamine-provoked ulcer, but inasmuch as histamine acts directly on the parietal cells, this is not a criticism of vagotomy in the treatment of peptic ulcer in man.

Hollander (56) described the insulin test for the presence of intact nerve fibers after vagal operations for peptic ulcer. A fractional gastric analysis is done after hypoglycemia of 50 mg. or less is induced with 15 units of insulin intravenously. A positive response to the insulin test, consisting of a distinct rise in the curve for free acidity, indicates that some uncut parasympathetic fibers still carry secretory stimuli from the medulla. A negative response indicates that all the fibers have been cut.

A series of 30 patients treated at the Duke Hospital by transthoracic vagotomy was reported by Ruffin (57) and Grimson (58). The left eighth or ninth rib was resected and 10 cm. sections of the vagus nerves removed. There were no fatalities, and all the patients were relieved of their symptoms with prompt healing of the ulcers. Half the patients complained of epigastric distention after eating, however, and 5 required subsequent gastrojejunostomy or pyloroplasty. The authors thought it too early to draw conclusions as to the lasting value of the procedure.

Moore et al. (59) reported a series of 15 patients with intractable ulcer treated at the Massachusetts General Hospital by transthoracic vagotomy, and advised that the diaphragm be opened to permit resection of the nerves well down on the stomach wall and thereby prevent regeneration. The operation is not indicated in cases of acute perforation, acute massive hemorrhage, or advanced cicatricial obstruction. The duration of relief following the operation is as yet unknown.

Weeks (60) reported the first 2 deaths associated with supradiaphragmatic vagotomy. In the first case the patient died of a perforated duodenal ulcer one month after vagotomy. This patient also had a bilateral thoracolumbar sympathectomy for hypertension, and this probably neutralized the effects of the vagotomy. The patient had no pain with the acute perforation. In the second case the patient died on the operating table following manipulation

and division of the right vagus nerve; death was the result of circulatory collapse.

Preoperative and postoperative care. Varco (61) stressed the effect of an adequate preoperative diet in lessening postoperative complications. He recommended a high protein, high carbohydrate, low fat diet before gastrointestinal operations with a daily intake of 5000 calories. Milk powder is stated to be a useful source of supplementary protein. Lund (62) presented an outline of the nutritional requirements of patients recovering from gastrointestinal operations, with particular emphasis on protein.

Postoperative complications. Leakage of duodenal stump. After a review of the literature on methods of closure of the duodenal stump in gastrectomy, Shapiro and Robillard (63) concluded that the most prevalent complication following gastrectomy is leakage of the duodenal stump. This is believed to account for most of the mortality, which ranges from 2 per cent to 30 per cent. The authors dissected 62 bodies, described the anatomy of the pancreaticoduodenal vessels, and concluded that the procedure of duodenal mobilization from the pancreas might devascularize the stump sufficiently to interfere with healing. They suggested inversion of the freed duodenum to the point of pancreatic attachment so that intact rami duodenales may provide adequate intestinal circulation.

The duodenum has a rich vascular anastomosis. Unless the inferior pancreaticoduodenal artery is ligated there should be no difficulty. Most duodenal fistulas are undoubtedly due to faulty and incomplete inversion and closure; this should seldom occur.

Dumping syndrome. Custer, Butt and Waugh (64) presented a clinical study of the dumping syndrome after subtotal gastrectomy. Symptoms of weakness, a generalized and unpleasant sensation of warmth throughout the body, cold diaphoresis of the face (especially the forehead), and cardiac palpitation after eating are the result of a rapid emptying of the stomach into the jejunum. Of 500 patients studied, 5.6 per cent complained of one or more of these symptoms; some obtained relief by lying down after eating, and many were finally relieved. This ultimate relief is explained by the theory that the jejunum becomes adjusted to the early deposit of food. It is recommended that patients be instructed to experiment with the following procedures for relief; to lie down after eating, to take ephedrine, $\frac{3}{8}$ grain with two or three soda crackers before meals, 30 cc. of cream or 45 cc. of olive oil before meals, six small meals daily, a dry diet, and 10 drops of dilute hydrochloric acid a half hour before meals.

Gastrojejunal ulcer. Wagensteen (65) attempted to determine the cause of postoperative gastrojejunal ulcer by experimental surgical procedures on dogs. He concluded that when gastric resection is performed, a long afferent jejunal loop invites the formation of stomal ulcer. Resection of less than 75 per cent of the stomach is

also stated to be a predisposing factor. We believe that an inadequate resection is a more important factor.

Evidence that antecolic anastomosis with a long jejunal loop does not predispose to the development of jejunal ulceration in human beings is presented by Kennedy and Reynolds (66), who performed 90 consecutive gastric resections without the formation of jejunal ulcer. The antecolic gastrojejunostomy is preferable to the posterior because it is quicker, easier, and safer in that there is less danger of injury to the middle colic artery. The authors concluded that in human beings the mucosa of the jejunum in the long loop as well as the mucosa of the jejunum closer to the stomach, is able to withstand the effects of receiving gastric contents directly.

Marshall (67) found that in a series of 289 resections for ulcer, 69 were for gastrojejunal ulcer. Of this group of 69 cases, stomal ulcer developed after gastroenterostomy in 60, after inadequate partial resection in 5, and after Finsterer prepyloric resection in 4. Jejunal ulcer was not related to the length of the jejunal loop. The author emphasized the importance of performing extensive resection with removal of the duodenal ulcer; gastroenterostomy should rarely be used except in carefully selected cases. Retained antral or pyloric part of the stomach predisposes to jejunal ulceration.

Fallis and Warren (68) found that 15 per cent of patients undergoing gastroenterostomy develop jejunal ulceration. In addition to the usual preoperative preparation for gastric resection, it is important to cleanse the colon thoroughly in case the jejunal ulcer is adherent to the colon, which may have to be opened. The author's technic is to detach the transverse mesocolon from the anastomotic area and then resect the involved portion of jejunum with its mesentery; subtotal gastrectomy is then done if it was not done previously.

Walters (69) reported that in 3 of 5 cases in which hemorrhagic and ulcerative gastrojejunitis occurred after gastroenterostomy was performed for congenital pyloric stenosis, removal of the gastroenteric anastomosis with resection of the stomach and a Billroth I (von Haberer) type of anastomosis between the proximal end of the stomach and the duodenum produced relief. The other 2 cases were controlled by a medical regimen.

Gastrojejunocolic fistula. The symptoms of diarrhea, steatorrhea, weight loss, anemia and malnutrition have been generally ascribed to the shunt of food from the stomach through the fistula to the colon. A clinical and experimental study by Renshaw et al. (70), however, indicates that this shunt is not the major factor in the production of the syndrome. Fistulas produced in 7 dogs and roentgenograms of 10 patients showed the barium meal passing through the small intestine rather than running directly into the colon. It is suggested that deranged digestive and absorptive functions of the small intestine may cause the clinical syndrome attributed to gastrojejunocolic fistula. This derangement is probably the result of damage to the intestinal mucosa caused by passage of colonic contents through the small intestine.

Joyce (71) suggested a plan for bad risk cases of gastrojejunocolic fistula in which the colon is separated and repaired and, instead of a complete new gastrectomy, the

existing anastomosis is interfered with as little as possible. A case is reported with recovery. Such a conclusion is not warranted on the basis of the material. Certainly the high mortality of the past in this type of surgery has been associated with the simple disconnecting operation.

CARCINOMA OF THE STOMACH

Diagnosis. Maimon and Palmer (72) reviewed 576 cases of gastric carcinoma at the University of Chicago, and found a trend to earlier diagnosis; 76.3 per cent were over 50 years of age, and 69 per cent were males. Symptoms were of less than three months' duration in 25 per cent, and less than six months in 53.7 per cent of the cases. Gastroscopy yielded the correct diagnosis in 84.6 per cent of the cases in which it was used; roentgenograms provided the correct diagnosis in 91.8 per cent of the cases in which they were employed. It is emphasized that neither gastroscopy nor roentgenography can determine resectability in any particular case.

Papanicolaou (73) found that cells stained from aspirated gastric juice may be used to diagnose carcinoma of the stomach. Of 9 cases studied, 2 gave positive smears. The diagnostic value of this test is based on the constant exfoliation of malignant neoplasms having a free surface. This test may prove to be valuable in early detection of cancer, but more studies need to be done to prove it.

Pathology. Schindler (74) proposed a classification of the gross types of gastric carcinoma as an aid to prognosis. Type I is the sharply limited polypoid tumor; Type II is a sharply limited ulcer with an elevated wall; Type III is ulceration not completely surrounded by a wall, and Type IV is the diffusely infiltrative tumor. In 7 cases of three-year cures following resection, 6 were Types I and II; in 4 five-year cures, all were Types I and II. It is claimed that by a combination of roentgenography and gastroscopy the gross type can be determined before operation and the relative surgical curability predicted.

Boyce (75) reported 36 cases of perforated gastric carcinoma at the Charity Hospital in New Orleans; 31 were males and 5 females. Only 6 left the hospital alive, of whom 2 had a gastrectomy. The diagnosis is usually difficult although the condition is not rare, and the diagnosis is not usually made before operation or autopsy. Gastrectomy is the procedure of choice but is not often possible because of the advanced stage of the lesion and the condition of the patient. The only solution to the problem is diagnosis before perforation occurs.

Schindler et al. (76) presented 4 cases of gastric leiomyosarcoma observed gastroscopically, and reviewed 94 cases from the literature. The cardinal findings are: (1) gastrointestinal hemorrhage leading to anemia; (2) epigastric or left upper quadrant pain, and (3) an upper abdominal mass. The preoperative diagnosis can be made by roentgenography or gastroscopy. Roentgen treatment is ineffective; 2 of

the patients presented survived resection. Resection of the stomach with leiomyomas is not especially difficult and should carry an operative mortality less than that for cancer.

Treatment. Lahey (77) discussed some points of value derived from long personal experience, in determining the resectability of cancer of the stomach with the abdomen opened. He emphasized the need for careful exploration by the surgeon before becoming committed to extensive resection. Brunschwig and Morton (78) suggested that increased palliation may be achieved in some instances in which direct spread of the tumor to the liver or spleen is excised. Cattell and Mosely (79) reported 2 cases of successful combined subtotal gastrectomy and resection of the transverse colon for cancer involving both organs by direct extension.

Many studies of total gastrectomy have been reported in the last five years. There is a steadily decreasing mortality and the indications for total gastrectomy have been well outlined.

Total gastrectomy. Moreland (80) reported a series of 6 total gastrectomies without fatality. Beaver (81) reported 1 case and advised the use of a Miller-Abbott tube in the efferent jejunal loop.

Transthoracic resection. Humphreys (82) reviewed a series of patients treated for carcinoma of the esophagus and gastric cardia at the Presbyterian Hospital in New York. Esophagogastrectomy with intrathoracic esophagogastrostomy or esophagojejunostomy was done in 12 cases, with a mortality rate of 50 per cent. Partial or complete gastrectomy with intra-abdominal esophagogastrostomy, esophagojejunostomy or gastrorrhaphy was done in 5 cases, with no postoperative fatality.

Tanner et al. (83) suggested the following advantages of preliminary laparotomy in the management of carcinoma of the lower esophagus and cardia: (1) ease in freeing the stomach and lymph nodes; (2) better mobilization of the jejunum; (3) better closure of the duodenal stump in total gastrectomy; (4) better determination of resectability, and (5) performance of a higher resection and easier anastomosis. There were 2 deaths in a series of 8 cases of transthoracic resection of the stomach.

Nagel and Menke (84) presented a series of 16 patients operated on at the Stanford University Hospitals for carcinoma of the lower portion of the esophagus and stomach. The transthoracic route was employed between the eighth and ninth ribs, without rib resection. The authors stated that this operation safely falls within the realm of general surgery and need not be limited to the thoracic surgeon. There was 1 death in 7 resections.

The combined abdominothoracic approach for carcinoma of the cardia and lower part of the esophagus was advocated by Garlock (85), who maintained

the advantages are better exposure and ease of manipulation, and a smoother postoperative course than with rib resection. With the patient on his right side, a 5-inch incision is made along the outer edge of the left rectus and the abdomen explored. If the tumor is resectable, the incision is extended upward and outward between the eighth and ninth ribs, and the diaphragm cut radially.

Results. Eliason and Witmer (86) presented a statistical analysis of 35 cases of gastric carcinoma between 1929 and 1935, and 114 cases from 1934 to 1944. Sixty-four per cent of the patients were male. It was found that in general the time lost between the appearance of symptoms and the first visit to a physician was not as great as the time lag between the first visit to a physician and referring the patient to a surgeon. Exploration was carried out in 91 per cent of the cases, of which 35 per cent were resectable, with a mortality rate of 17 per cent. There were only 3 five-year survivals (2 per cent). Only 1 total gastrectomy was done. It is suggested that the only way to better these results would be to decrease the time lag and to do more total gastrectomies.

Lawrence and Kay (87) compared two series of cases in the decades between 1920 and 1940, and found that patients did not report to the hospital earlier in the latter group; however, resectability increased and operative mortality decreased. There was a 40 per cent loss owing to obvious inoperability or patient's refusal of operation. The lesions in 35.5 per cent of those explored were not resectable; the operative mortality was 8.8 per cent, while 9.3 per cent of the patients gradually declined and died soon after leaving the hospital. Of 208 patients admitted, 4.4 per cent were alive and symptom free after five years.

Maimon and Palmer (88) reviewed 576 cases of gastric carcinoma, with laparotomy in 83.5 per cent. Of the explored cases, resection was performed in 52.1 per cent, with a mortality of 26.1 per cent. The postoperative mortality for subtotal gastrectomy was 20.8 per cent, for total gastrectomy 43.7 per cent, and for transthoracic resection 52.8 per cent.

Otaiza (89), in Chile, reported a series of 332 patients, of whom 75 per cent were male. Operation was performed on 268 patients, of whom over 50 per cent (138) had a resection, with a mortality of 20 per cent. Resectability is greater in persons who have had symptoms over a year, possibly because they have slow-growing lesions.

In general, exploration is carried out in about half of the cases coming to surgery, and about half of these can be resected; in other words, about 1 in 4. Earlier detection of cancer of the stomach is imperative if progress is to be made in control of the disease.

MISCELLANEOUS ENTITIES

Congenital hypertrophic pyloric stenosis. Donovan (90) reported a series of 507 patients treated by the Rammstedt operation, with 9 fatalities (1.8 per cent). The condition was seven times more common in boys than in girls. Vomiting is always the first symptom and usually begins between the second and fifth weeks. Tumor, consisting of hypertrophied pyloric circular muscle is pathognomonic and may be felt in every case in the right upper quadrant of the abdomen. A follow-up was obtained in 82 per cent of the patients, all of whom were permanently cured.

Ladd et al. (91) reviewed a series of 380 cases between 1939 and 1945 with 4 deaths (1.05 per cent). There were no deaths in 225 cases during the last three and one half years. Eighty-five per cent of the patients were male. The vomiting was explosive, began between the second and fifth weeks, and contained no bile. Dehydration and alkalosis were treated with 3 ounces of fluid per pound of body weight per day, and surgical interference was often delayed for two or three days. The authors describe the details of pyloromyotomy, and present their postoperative regimen.

Jacoby (92) reported 50 successive patients treated without a fatality, and advised that when vomiting begins after the fourth week, medical treatment is preferable to surgical treatment.

Congenital duodenal atresia. Five cases of complete duodenal obstruction in the newborn were reported by Hicken et al. (93) with 4 deaths. The various anatomical abnormalities encountered, the symptoms, diagnosis, and treatment are discussed. In each case there was atresia of the duodenum.

Cardiospasm. The etiology of cardiospasm is still in dispute. According to Bell (94), dilatation is the simplest procedure and should always be tried. Ten cases of esophagogastrostomy with good results are reported; there were no deaths. Eight patients had complete relief, and 2 required a subsequent operation to correct the anastomosis.

Grimson et al. (95) discussed the etiology of achalasia and reported a series of 9 patients treated by esophagogastrostomy, with no mortality and improvement in all cases. The esophageal dilation is secondary to chronic obstruction and is not idiopathic; it is believed that the fundamental pathology may reside in lesions of the myenteric plexus. A transabdominal approach is used, with the esophagus mobilized and the dilated segment pulled down through the hiatus. Incisions are made into the esophagus and fundus, and an anastomosis performed.

Hiatus hernia. Mendelsohn (96) reported 16 cases of hiatus hernia of the stomach found in 1000 consecutive roentgenologic examinations of the upper gastrointestinal tract. There were 8 males and 8 females, and most of the patients were over 50 years of age. The condition was asymptomatic in 3 cases.

Tumen and Yaskin (97) stated that hiatus hernia may produce pain in the back when the body is supine or prone.

Hereditary telangiectasia. Kushlan (98) reported a case with gastrointestinal bleeding, in which rutin therapy seemed to give good results. The criteria for

diagnosis are: definite heredity, visible telangiectases with pathologic distribution and a tendency to bleed from the lesions. Epistaxis in childhood is often the first manifestation, and gastrointestinal hemorrhages usually begin in the fourth decade. The lesions are usually noted in the stomach and in the sigmoid colon. They may also be noted in the small bowel and usually are so widespread that resection is of little value.

Hodgkin's disease. About 20 cases of isolated Hodgkin's disease of the stomach have been reported. Browne and McHardy (99) reported 2 cases of this rare entity and stated that resection followed by roentgen therapy should effect a cure. Samek-Ludovici (100) reported a case in Italy with symptoms similar to those of carcinoma; the typical tissue of Sternberg was found replacing the mucosa and infiltrating the muscularis. A resection was performed but the patient died three months later of a recurrence.

Angioneurotic edema. Eleven cases of angioneurotic edema in which gastroscopy, revealed edema of the stomach are reported by Chevallier (101). Strawberries, chocolate, and fish were the most common precipitating factors.

Acute gastric dilatation. According to Beck (102), acute dilatation of the stomach is caused by duodenal obstruction, usually where the superior mesenteric artery crosses over. Predisposing factors include emaciation, ptosis of viscera, short mesentery, lordosis of the lumbar spine, and collapsed intestine as in wasting diseases. The symptoms are bile-stained vomitus and distention. Roentgenograms show dilatation of the first and second parts of the duodenum. Most cases can be managed successfully with Wangensteen suction and elevation of the foot of the bed or the knee-chest position; operation is rarely necessary.

Pancreatic heterotopia. Waugh and Harding (103) examined about 800 stomachs after subtotal gastrectomy and found 5 in which a pancreatic rest in the region of the pylorus was the only lesion present. It may be responsible for the symptoms of peptic ulcer by causing spasm or obstruction. Ectopic pancreatic tissue in the gastric wall is not uncommon. It may be confused with carcinoma.

Transpyloric prolapse of mucosa. Scott (104) believed that prolapse of gastric mucosa into the duodenal bulb is of clinical significance. The condition occurred in 14 (1.04 per cent) of 1346 cases in which upper gastrointestinal series were done in a naval hospital, and 3 cases were proved by operation. The symptoms were intermittent gastric distress, cramping pains (14 patients), relief from food (10 patients), sense of fullness, bloating and heartburn (9 patients), and nausea and vomiting (4 patients). Additional complications were bleeding (3 patients), gastric retention (1 patient), coexisting duodenal ulcer (1 patient), and gastric ulcer (1 patient). The roentgen diagnosis consists mainly of the demonstration of a characteristic mushroom or cauliflower-like filling defect in the base of the duodenum, not to be confused with the deformity caused by ulcer. The recommended treatment is surgery (excision and pyloroplasty) for the severe cases, especially those with bleeding, and medical therapy for the others.

MacKenzie et al. (105) reported 2 cases of prolapse of gastric mucosa into the duodenum, diagnosed by the roentgenogram, and stated that there is no charac-

teristic syndrome. A longitudinal incision is made into the antrum and proximal duodenum. The redundant mucosal fold is excised. This condition is met with occasionally and seldom demands surgery. Usually simple medical measures of diet will control the symptoms.

Diverticula. Five cases of gastric diverticulum were reported by Walters (106); all were symptomatic and diagnosed by the roentgenogram. Four patients were relieved by removal, and the fifth by inversion, of the diverticulum. In all cases the diverticula extended from the posterior wall of the stomach, just off the lesser curvature. In 4 cases the approach was made by dividing the gastrocolic omentum and gastrolienal ligament, and in 1 case the diverticulum was approached through the gastrohepatic omentum. The pain is said to be caused by retention of food in the diverticulum with gastrospasm, as well as a local gastritis.

Resnick (107) reported 3 cases with ulcer-like symptoms, found in 1000 roentgenologic examinations of the stomach.

According to Moses (108), the usual site of a gastric diverticulum is on the posterior wall near the lesser curvature in the cardiac region. One out of three are symptomatic; there is no typical syndrome. He reported a case of rupture and bleeding into the peritoneal cavity, the first case of this nature recorded.

We have reviewed many more papers than are presented here but we feel that these articles were of insufficient general interest to warrant undue lengthening of this review. A complete reference list (109–154) of all articles for the year is appended, and these may be referred to if desired.

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THE PANCREAS: CONTRIBUTIONS OF CLINICAL INTEREST MADE IN 1946

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During the year 1946 a larger number of reports on diseases of the pancreas have appeared than ever before. Part of this has been due to the greater availability of foreign journals in which many of these observations are recorded, part to the increase in the number of accurate reports recorded in local and state journals. These papers are fairly well distributed among the various topics discussed in previous reviews with perhaps more attention paid this past year to cystic disease of the pancreas. There is also a continuation of increased interest in the surgical treatment of carcinoma of the pancreas by radical operation. As in previous reviews, consideration will be confined entirely to diseases and function of the external secretions of the pancreas. The islet tissue will not be included. Only reports containing objective data were selected for review. The delay in the appearance of this review for 1946 has been due to the delay in the appearance of the cumulative index, the last half of which was not available until the latter part of 1947.

ANATOMY AND PHYSIOLOGY OF THE PANCREAS

Another study of the relationship of the pancreatic and bile ducts of the human has been recorded (56) based on 250 dissections at autopsy. The variations found were somewhat different from those previously recorded in the literature. For example, a rather large number, 24%, were found to have separate openings for the pancreatic and bile ducts. On the other hand, in only 18% were the ducts found to join in such a way so that a complete block at the ampulla would convert the two ducts into a common channel. It has been long known that such a common channel may also be formed by spasm whenever the septum separating the two ducts ends sufficiently proximal to the sphincter. Of additional interest was the fact that in 89 of 100 cases there was an intraglandular communication of the main pancreatic duct and the accessory duct.

An interesting microscopic study of the anatomy of the acinar cells of the pancreas was made (16) by analyzing photometrically the absorption spectra with ultraviolet light. This enabled interesting observations to be made of the relative concentration of protein granules in the various zones of the cytoplasm. The basal part of the cytoplasm showed a maximum absorption at 2600 Angstrom units which indicated the presence of nucleotides. Another microscopic study was made (32) of the alkaline phosphatase activity of the pancreatic cells by histo-chemical methods. The guinea pig and rat were found to contain no

alkaline phosphatase, but in the dog this substance was found in the epithelial cells of the duct system. The same was true in the rabbit but to a lesser extent. The islet cells contained alkaline phosphatase only in the dog. There were no human studies. An interesting study (21) showed microscopic changes in the pancreas produced by a low protein diet in male albino rats. As compared with control diets containing 25% protein, the experimental animals after a period of about 3 to 7 weeks on a 10% protein diet showed degenerative changes in the acinar tissue and loss of cytoplasm. Parallel with this change was definite fatty infiltration and degeneration of the liver.

Pancreatic secretion in 24 dogs with pancreatic fistulae was studied (65) using the effect of atropine and hyoscyamine as the base line. The effective dose of these drugs was first established which would block secretory endings of the vagus nerve. The pancreas was then stimulated by various means and these drugs again given. They still showed a definite inhibitory effect when pancreatic secretion was stimulated by soap or hydrochloric acid instilled into the intestines. However, when secretin intravenously was used as a stimulant, the inhibition was very much less marked. The use of peptone produced equivocal results in that, when this material was present in the intact intestines, the inhibitory drugs failed to show any effect in 7 out of 10 experiments. On the other hand, when the peptone was instilled into an isolated Thiry loop, the drugs abolished the secretion as they did in other experiments. An attempt was made (62) to determine a substance which was selectively secreted by the pancreas. In this case, radioactive cobalt was injected intravenously and found not to be eliminated in the pancreatic juice. Of the injected salt 5% was present in the bile collected over a 72 hour period. An electrophoretic analysis (44) of pancreatic juice collected from a fistula in 6 hours revealed that there were at least 4 or 5 different protein components depending on the dog used but independent of stimulation or total protein concentration. These fractions were probably all globulins. No evidence of albumin was obtained.

An intriguing idea has been advanced (27) that some of the external secretion of the pancreas may originate from duct epithelium. This is based upon experiments in which 6 alloxan treated dogs, 4 of which were diabetic, required much larger doses of secretin and pancreozymin to evoke pancreatic secretion than normal dogs. Histological study in one dog showed evidence of damage to the intraductal epithelial cells. However, another explanation of these findings might be the depressant effect of alloxan in the acinar tissue, even though no microscopic changes were apparently observed in the acini.

The function of the external as well as the internal secretion of the pancreas was subjected to an interesting study (67) in 4 patients who had survived successful total pancreatectomy; 2 for islet cell tumors, 1 for carcinoma of the head of the pancreas, and 1 for chronic pancreatitis with calcification. The diabetic

state became established 18 to 24 hours after operation. The effect on digestion and absorption was very definite inasmuch as the stools became bulky and light in color, fecal solids increased from 2 to 3 times normal. Fat made up 45% to 50% of the solids, protein 30% to 45%. There was no demonstrable evidence of hepatic insufficiency. Although plasma lipoids in pancreatectomized dogs fell to about 50% of normal the 20th week, no such change was observed in the human.

PANCREATIC FERMENTS

Increases in the blood amylase was found in a number of patients with uncomplicated mumps (74). There was also an increase in the urinary amylase; the increase paralleled the morning temperature. In the 15 cases studied, the increase was observed from the 3rd to 6th day of the disease. There was only 1 case of elevated blood amylase after the 6th day and this patient had clinical evidence of pancreatitis. Confirmation of an old observation regarding the effect of obstruction of the pancreatic duct on blood amylase was made (24) in 4 cats who were subjected to complete pancreatic obstruction and observed for 8 months. Both the serum amylase and lipase rapidly increased and then showed a definite decrease 1 to 3 months after ligation. In 1 animal autopsy showed a completely atrophic pancreas and in 3 others, almost complete necrosis. Yet in all of these cases the amylase and lipase concentration remained at a normal level, suggesting that these ferments have a source outside of the pancreatic acini. An extensive study of blood amylase (52) in normal humans as well as patients with pancreatic disease was carried out. The author, apparently, was unaware that previous observors had made similar studies and drawn the same conclusions. The method used for measuring amylase was only partly quantitative in that the activity was measured in terms of 1+ to 4+ using a cuprous oxide precipitation method. Obviously, such a method of measurement is inferior to one based upon quantitative amounts of sugar produced by the amylolytic material. Of the patients who had normal blood amylase concentrations, only 1 was shown to have pancreatitis. The relationship of the disease to the time of measurement of the specimen was not mentioned. In 7 patients a decreased amylase activity was found; all were patients with chronic wasting disease but with no evidence of pancreatitis. In 9 patients with only slightly decreased activity, there was no true evidence of pancreatic disease. In 7 patients with moderately increased activity, the pancreas was found to be involved in every case. In 9 patients the amylase was markedly increased and pancreatitis was proved in all.

The discoverer of lipocaic (19) studied the effect of a pancreatic extract on the liver lipoids of rats on a basal diet known to produce a fatty deposition of about 28% in the liver after 20 days. It was found that 140 mg. of the unfiltered

pancreatic extract was able to prevent this deposition of lipoids. The same was true of filtered pancreatic extract, whether the extracts were given by mouth or subcutaneous injection. On the other hand, 164 mg. of inositol daily was followed by no significant difference, i.e., the total hepatic lipoid remained at 30%. The authors conclude that inositol is not the active principal in beef pancreas which prevents dietary deposition of fat in the liver in rats.

ACUTE PANCREATITIS

Of the many reports on acute pancreatitis, some are still based only on the finding at autopsy or at operation. Apparently many observors are still unaware of the value of blood or urinary amylase and lipase determinations in the clinical diagnosis of this disease.

In a series of 21 cases (34) the point is made that this disease was present in old individuals, inasmuch as the patients averaged 57½ years of age. Apparently the diagnosis was made in all cases at autopsy. In a British report (23) 13 cases of acute pancreatitis were observed over a 4 year period, 1941 to 1944. Of these, 10 were submitted to operation, the pre-operative diagnosis being perforated ulcer, peritonitis, cholecystitis and intestinal obstruction. No mortality figures were cited. Diagnosis was based on the findings at operation or autopsy. In only a few cases was urinary amylase measured and found to be elevated. In a large clinic in this country (54) 20 cases were observed over a 12 year period. Of interest was the fact that 5 were operated upon of which only 3 recovered. Of those who were not operated upon and died, the diagnosis was established at autopsy. The author emphasizes the importance of serum amylase determinations for diagnosis. An analysis of 160 autopsy records (42) in which acute pancreatitis was found revealed a slight preponderance of male over female and an almost exclusive incidence of the disease beyond the 4th decade of life, only 11 of the cases appearing under the age of 30. Cholelithiasis as an associated lesion was found only in patients above 30 years of age and predominantly among females rather than males, the incidence reaching a high figure of 90% in the latter group and only 50% in the former group. In none of the decades of life above 30 was the incidence of cholelithiasis below 28%. In a Canadian hospital during a 7 year period, 1938 to 1945, 36 cases of acute pancreatitis were studied (22). A bedside diagnosis was made in only 6 of the 36 patients. Although blood amylase was not studied, urinary amylase was elevated at one period or another in all of the 18 cases in which it was done. The mortality was confined almost entirely to those with acute hemorrhagic disease; 15 of the 17 cases in this category ended fatally. In only 12 of the 36 cases was operation carried out. Presumably the diagnosis was made either at operation or at autopsy.

A series of single case reports of acute pancreatitis are cited because each

exhibits some interesting variations. In 1 case (10) a massive ecchymosis appeared in the abdominal wall. The patient was treated conservatively until a mass developed in the left hypochrondrium. Operation was then performed and a tremendous extravasation of blood found throughout the lesser peritoneal cavity, which was drained. This blood contained increased lipase activity, 5 times the normal value. Abdominal wall discoloration is an exceedingly rare manifestation of acute pancreatitis. Another case is described (33) in which many attacks undoubtedly of pancreatic origin had been present for 10 years uninfluenced by cholecystectomy. During one admission the patient had mild tetany during the attack but no blood calcium studies were made. This is of interest in view of the observations reported last year of the influence of pancreatitis on calcium metabolism. Another interesting case (14) was described in which at operation a localized pancreatitis with hemorrhage confined to the tail of the gland was found; excision including splenectomy was done. An undoubted case of pancreatic edema (35) was described in a female, age 40, in whom at operation only fat necrosis was seen. The patient was discharged 77 days after operation during which merely a cholecystostomy was done. Another case of massive hemorrhage profusely involving the pancreas was described (41) in which cholecystostomy only was carried out. The patient developed severe diabetes in the first month after operation but this improved, though he remained diabetic for a period of 7 years afterward. A case of recurrent pancreatitis in a 33 year old male was described (26) in which operation was not carried out. Diagnosis was readily made by observing the elevation of amylase in the urine and glycosuria with each attack. Another case is described (9) in which during 1 attack, the diagnosis was made by finding a slight increase of amylase in the blood. A second attack 2 months later in spite of cholecystectomy resulted in the patient's death. At this time the amylase was very low.

CHRONIC PANCREATITIS

A most important study of chronic pancreatitis particularly its relation to previous attacks of pancreatic inflammation has appeared (8), based upon a meticulous and long continued study of 21 cases. The authors use the term "chronic relapsing pancreatitis", the clinical picture consisting of recurrent attacks of pancreatitis of varying severity. In 13 of the cases there were definite transitory disturbances in acinar and insular function. Yet in spite of the frequency of attacks in many cases, in nearly half calcification, diabetes or steatorrhea did not occur. The serum enzyme levels were elevated during the attacks and normal between attacks. In 3 of the cases a diabetic type of glucose tolerance curve was observed during an attack. In 3 other cases, prominent changes in insular function and acinar function were produced lead-

ing to clinical diabetes and evidence of external pancreatic insufficiency. None of these cases showed calcification. The remaining cases showed variations in these factors, i.e., insular function, excretory function, and calcification. Of particular interest is the fact that autopsy observations were made on some of these cases and definite evidence was adduced to show that the previous attacks of pancreatitis, at least in some instances, were actually of the necrotic variety, as shown by areas of resolving necrosis in the pancreatic gland. This is probably the first observation in which the possibility of an attack of pancreatic necrosis which resolved spontaneously has been demonstrated. The treatment of this type of case is discussed in great detail and as might be expected, would depend on the individual problem of the individual patient and include both medical and surgical measures, the latter consisting of removal of pancreatic calculi, gastro-enterostomy for obstruction and even total pancreatectomy in the refractory cases.

A more traditional type of analysis of 26 cases of chronic pancreatitis has been reported (63) based presumably upon the clinical picture alone; although in many of the cases pancreatic enlargement was demonstrated by a lateral view of the abdomen in the x-ray with a contrast medium of barium or air in the stomach in some cases. The most constant objective sign was an increased amount of fat in the stool. No elevation of the amylase of the blood or urine was found, but these patients exhibited no acute phase. The secretin test showed a reduced amount of amylase in the pancreatic juice in only 3 cases. A similar but much less convincing series of 79 cases of chronic pancreatitis was reported (40) based upon a variety of anatomical and clinical observations made at operation. It is difficult to evaluate the clinical manifestations in the terms of the anatomical findings in this particular report. Although the author reports that operation in most cases consisted of cholecystostomy, in several splanchnectomies were done with apparently good clinical results.

ABERRANT AND ANNULAR PANCREAS

An unusually large number of these congenital anomalies have been reported during 1946. One report which reviewed the literature also contained 41 microscopically proven cases (4). Of these, 25 probably produced symptoms inasmuch as they were all found in surgical specimens. Many of them, however, were observed at autopsy as an incidental finding. Over 70 per cent of them were found in the stomach, duodenum or jejunum, and nearly half contained definite islets of Langerhans. Over half were limited to the submucosa and 76 per cent showed evidence of glandular function, as shown by staining methods. In another report (69) 5 cases of aberrant pancreatic tissue were found in the stomachs of approximately 800 specimens following subtotal gastrectomy. The author assumes that this tissue was responsible for the

symptoms inasmuch as no other lesion in the stomach was found in these 5 instances. Obviously another diagnosis had been made previous to operation, presumably ulcer or carcinoma. In another report (53) 2 cases of aberrant pancreas in the antrum of the stomach were described. In one of them the lesion was responsible for a delayed emptying of the stomach. The other was an incidental finding. Both produced filling defects in the antrum on gastrointestinal x-ray series. However, the diagnosis in both cases was made only after the removal of the specimen. In a series of 3 cases (56) x-ray showed definite findings in the stomach which at operation proved to be aberrant pancreas. The patients were aged 31, 55 and 51. In one case a gastric resection was performed and in the two other cases, the nodule itself was removed with apparent relief of symptoms. In an interesting case report (7) a benign single polyp was found in the prepyloric region of the stomach of a 5 year old boy which prolapsed into the duodenum and caused obstructive symptoms. The polyp was excised and proved to contain aberrant pancreatic tissue. The recovery was uneventful and symptomatic relief was complete. One case was reported (44) in which the patient was operated upon with a clinical diagnosis of cholecystitis, the gallbladder was found to be enlarged, thick walled and tense. The removed organ showed aberrant pancreatic tissue in the gallbladder wall which presumbably had been responsible for cholecystic obstruction. Two cases (37, 47) were merely reports of aberrant pancreas, both in the duodenum, which were incidental findings at autopsy, although in one case there was a likelihood that the lesion may have been responsible for some inflammation adjacent to it in the duodenum.

Annular pancreas. One reported case (25) showed on x-ray examination before operation dilatation of the stomach and first part of the duodenum due to an obstruction. At operation a hard, annular band over the distal part of the second portion of the duodenum was found, one inch wide and one and a half inches thick. Part of the ring was resected and the duodenal obstruction relieved. By 8 weeks after operation the patient was relieved of symptoms but there was still roentgenological evidence of 24 and 48 hour retention, although the patient took a regular diet without difficulty. The patient also had an incompletely rotated cecum.

PANCREATIC CYSTS

A number of reports of pancreatic cysts have appeared which, however, seem to add very little to what is already known of this condition. In one case report (55) the patient was operated upon for a palpable mass in the upper epigastrium; symptoms consisted only of 2 liquid stools a day. The mass proved to be a cyst of the pancreas which was marsupialized and drained; the patient died several days after operation. The influence of trauma and of

acute infection on the pathogenesis of the pancreatic cyst is shown by a report of 7 cases (74) in which an antecedent history of injury was obtained in 3, of acute pancreatitis in the rest. Trauma was also the instigating factor in another report (66) in which the patient was kicked in the abdomen two weeks before admission and at operation an effusion was definitely demonstrable into the lesser peritoneal sac which contained bile as well as pancreatic ferments, although no injury to the biliary tree could be demonstrated. The patient was 23 years old, and made a relatively uneventful recovery. The bile noted was obviously due to the fact that the pancreatic and the bile ducts communicated with each other. That pancreatic cysts follow acute inflammatory processes in the pancreas is also shown by a report (64) of 5 cases in which a definite previous attack of epigastric pain had been present. In one case the cyst was discovered 10 years and in one case 6 weeks after the first attack. The surgical treatment of pancreatic cysts is discussed on the basis of 9 cases (1) 5 of which were drained, 2 of them subjected to an anastomosis between the cyst and the jejunum, and 2 implantation of the sinus tract after drainage into the jejunum was carried out. The results in all were satisfactory. An interesting case is described (30) in which the fistula following drainage of the pancreatic cyst persisted for 4 months before closure. A radio-opaque substance was injected into the fistula and a complete x-ray visualization of the entire pancreatic duct system was obtained, showing again that cysts communicate with the pancreatic ducts. The x-ray diagnosis of pancreatic cyst is described on the basis of 13 cases observed during a 10 year period (31). The radiologic findings are based almost entirely upon displacement of adjacent organs and widening of the duodenal curve.

PANCREATIC LITHIASIS

A thorough study of over 13,000 sections of the pancreas (13) revealed 58 cases of pancreatic lithiasis or an incidence of 0.43 per cent. Disease of the liver or bile ducts was present in 64 per cent, icterus in 17 per cent, diabetes in 28 per cent of the 58 cases. This author also examined the pancreas from 153 cows; 3 of them showed multiple duct stones and enterogenous bacteria. One case of pancreatic lithiasis in a 76 year old man is reported in which the findings at autopsy showed an actinomycotic infection associated with the stone.

An interesting case of pancreatic lithiasis was reported (20) in a 36 year old male in whom recurrent attacks of severe epigastric pain were responsible for 2 exploratory laparotomies, presumably for intestinal obstruction, although none was found. The diagnosis was finally made by x-ray visualization of the stones of the pancreas. The patient eventually developed mild diabetes but had no steatorrhea. Operation was carried out on a patient 23 years old (48) in which two thirds of the pancreas was removed with an uneventful recovery,

although no follow-up observations were recorded. The diagnosis was readily made by observing calcification of the pancreas on x-ray. Another successfully operated case was reported in a 35 year old male (11) in which the patient also had a duodenal ulcer of the second portion of the duodenum producing massive hemorrhage on several occasions. After excision of the ulcer, at the base of which a pancreatic fistula was found and probed, the stone was extracted. The recovery from operation was uneventful, but there was no follow-up recorded. Two cases of pancreatic lithiasis were reported (70) in which improvement followed medical treatment, i.e., a low fat diet and an atropine preparation. Both patients had recurrent attacks of upper abdominal pain, reflex gastric disturbances, steatorrhea and characteristic x-ray findings. Another single case report (43) is described in which duodenal drainage revealed normal ferment activities. The patient showed characteristic x-ray findings; diagnosis was first suspected after a 15 month history of recurrent abdominal pain when he was discovered to have glycosuria.

CARCINOMA OF THE PANCREAS

The diagnosis of carcinoma of the pancreas, particularly in the body, continues to puzzle observers. In one report, the diagnostic significance of back pain is discussed (38). The author also cites a case in which colicky pain in both lower quadrants was present for only 5 weeks, yet at operation an extensive inoperable carcinoma of the body of the pancreas was found, illustrating the hopeless situation which may be present even after a short history. The author found that serum amylase and lipase determinations were elevated in some of these patients and may be of some diagnostic value.

The author of the modern operation for resection of the head of the pancreas (73) has reviewed his observations, emphasizing the importance of silk technic in eliminating many of the early complications. He advised using the common duct rather than the gallbladder for anastomosis and recommended implanting the pancreatic duct into the intestines. Although a large number of experiences with radical resection of the head of the pancreas and duodenum followed by a variety of anastomoses have been presented in 1946, it is clear that the mortality is still high and the end results poor. One report (68) contained the details of 30 patients who were subjected to radical excision during a period of 5 years. The total hospital mortality was 20 per cent; of these, 6 patients with carcinoma of the ampulla are known to be living and well up to 24 months following operation. In patients with carcinoma of the head of the pancreas, however, but 6 out of 15 who survived operation are well for 3 to 7 months after operation, and only one is alive at 3 years, but has definite evidence of recurrence. In another report of 5 cases (6) the importance of implanting the pancreatic duct was shown by the fact that, when this was not done, a pan-

creatic fistula followed which in one case was still draining seven months after operation. In a very extensive report 82 cases of carcinoma of the pancreas were analyzed (49) of which 30 had palliative operations, 19 exploratory operations and 9 radical resections. Of the 9 there were 2 postoperative deaths. Of the 7 who survived only one is alive 24 months after operation, but has an enlarged liver undoubtedly due to metastases. Two of the patients developed pancreatic fistulae, one of which persisted only 2 weeks. Two radical resections were described by a British surgeon (51) both in patients 50 years of age without operative mortality. One patient remained well one year after operation, both developed pancreatic fistulae, one of which lasted only one month. A single case was reported by a Canadian surgeon (61) in which the patient was well 4 months following operation; a pancreatic fistula developed which closed spontaneously, and diarrhea occurred which was controlled with pancreatin. A series of radical resections was reported (15) in 14 patients, followed by a 29 per cent mortality. Of the 10 survivors 5 died an average of 5 months after operation; 5 remained living and well up to a period of 12 months.

An unusual case of carcinoma of the pancreas is reported (60) in which the diagnosis was made at the time of laparotomy by biopsy in 1941. No procedure was carried out at this time; 4 years later the patient died and showed a tumor which was still localized and resectable. Another single case of a large tumor 12 x 8 x 6 cm was reported (59) removed from the body of the pancreas in a 48 year old female who had a known palpable mass for several years. The tumor was microscopically malignant and proved to be an islet cell tumor. However, there were never any symptoms of hypoglycemia and several glucose tolerance curves were normal. Local recurrence and death with mesenteric thrombosis occurred 3 years and 10 months after operation.

CYSTIC FIBROSIS OF THE PANCREAS

A much larger number of papers have been devoted to presentation of data on this condition during 1946 than in any previous year, although very little that is new seems to have been added. A large series of 25 cases were described (39), 18 of which died at ages from one week to 7 months. Of those living none has recovered, but some seemed to have improved on a high protein, moderate fat and carbohydrate diet, pancreatin by mouth, penicillin as an aerosol inhalation (1 cc. containing 1800 units) and 100,000 units of vitamin A intramuscularly several times a week. Seven of the patients had siblings that had died from the same condition; one patient had two siblings and one had had five with the same disease. The question of the hereditary nature of cystic fibrosis of the pancreas has been discussed (3) with a study of the genetics in 48 cases in which a definite history had been obtained of siblings with the disease, and from 56 cases collected from the literature. While the incidence among siblings

approximated 25 per cent, as might be suspected of a Mendelian recessive characteristic, it appears that more than one factor is necessary for its appearance. The author concluded that it must be a relatively infrequent hereditary trait. In a report (17) of identical twins, both of whom exhibited cystic fibrosis of the pancreas, both developed pneumonia at 4 months of age and in both there was approximately 50 per cent of fecal fat, and duodenal drainage revealed a complete absence of any of the pancreatic ferments.

Two long review articles have appeared. In one of them (75) a series of 22 cases was also described, based on findings at autopsy. The oldest patient was $2\frac{3}{4}$ years of age. The second article (5) reported 2 cases, both proved at autopsy, although one of them had been recognized before death. Analysis of duodenal contents were made in 5 cases including 2 normal and one with celiac disease. The 3 controls showed a very definite response in regard to the volume of duodenal secretion, which increased after the instillation of hydrochloric acid into the duodenum, the tryptic activity increasing normally. The 2 patients with fibrocystic disease showed very little increase in the volume of duodenal secretion and there was very little or no tryptic activity in the material aspirated. Along a similar line the absorption of vitamin A was measured in 3 infants with cystic disease of the pancreas (50). There was no increase in absorption when 25 mg. of prostigmine bromide was administered orally 3 times a day for a period of 2 to 7 months. There was no rise in the vitamin A level in the blood serum even when the drug was given subcutaneously. However, the drug did produce active peristalsis in patients with this disease, but the course was no different with its use.

In a report of 4 cases (58) the association of cystic fibrosis of the pancreas with meconium ileus was pointed out. The latter condition, as noted in previous reviews, apparently is due to the absence of pancreatic ferments which normally digest the meconium present in the intestinal tract. In only one of the four patients described was there any clinical improvement, the patient gaining weight and doing well after about 6 weeks by using one or more of the various methods of therapy including pancreatin, which have been described elsewhere. A report from Switzerland (71) describes 3 typical cases of cystic fibrosis of the pancreas, all of them being observed at autopsy and showing the usual clinical pictue already described by many. One case is reported (12) in which some clinical improvement followed the use of a high protein milk, low fat and carbohydrate diet, banana powder, vitamins and one gram of pancreatin. The child attained the age of 15 months at the time of the report with body weight of 20 pounds, but still had 6 to 10 stools a day and many râles in the chest. Another case is described (29) which seemed to do well under conservative treatment until 15 months of age when the patient developed increased diarrhea, large oily stools 8 to 10 times per day. Measurement of the

total fecal fat was made and showed that when the patient was given liver extract and vitamin B complex on a controlled constant diet, the fecal fat fell from 65 per cent to a level of 34 per cent 3 weeks later. When the liver extract and vitamin B were stopped the level of fecal fat returned to 56 per cent. Eventually, however, the patient developed a bronchopneumonia and died; typical findings were noted at autopsy. Another single case report (36) was that of an infant 11 months old whose diagnosis was made at autopsy and who had exhibited typical respiratory and intestinal symptoms. Of interest was the fact that one brother and possibly two died from the same disease previously. The author in his experience had observed no child with this disease who had been known to survive beyond the period of 14 years of age. Observations of total fat in the stools showed 58 per cent, of which split fat was 35 per cent, neutral fat 33 per cent and soap 30 per cent.

A radiological study (46) in 50 patients with cystic fibrosis of the pancreas showed that 60 per cent of the cases presented evidence of meconium ileus on the basis of dilatation of the small intestinal loops in the abdomen and disturbed motor function. Pulmonary changes included bronchial plugging without superimposed infection or definite evidence of infection present often with signs of bronchiectasis. In a study (18) of the respiratory tract infections associated with cystic fibrosis of the pancreas, 15 cases are described treated with penicillin aerosol. Of these 6 died mostly in the early part of the series. The others have all seemed to improve, some now with no symptoms or signs of pulmonary disease.

The physiological absorption of protein was studied (72) in a patient with cystic fibrosis of the pancreas in whom the amino acid level in the blood was observed following the ingestion of a test dose of either whole or hydrolyzed protein. Whereas in normal individuals there was a definite rise in the blood amino acid nitrogen usually within an hour or two after the ingestion of whole protein, in the case of cystic fibrosis of the pancreas, there was a perfectly flat curve from 3 to 5 hours. On the other hand, with hydrolyzed protein, elevation of the amino acid nitrogen in the blood was observed in all patients.

One case is reported (28) of an adult with presumed cystic fibrosis of the pancreas who died at the age of 35 years. This diagnosis was based on the findings at autopsy, the patient having suffered from painless jaundice and anorexia 3 years previous to death. It is difficult to be sure, however, that this was a true case of diffuse fibrosis such as is seen in infancy. Definite fatty change in the liver was found.

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SIXTY YEARS OF VAGOTOMY; A REVIEW OF SOME 200 ARTICLES

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Because of the great interest today in vagotomy, it seems worth while to sum up, briefly, most of what has been learned about the results of this operation in animals and man. I have not tried to quote here all the good writings on the subject because that would entail needless repetition of much that can be found in the several review articles prepared in the past and listed here; what I have tried to do is to sum up briefly all important researches on animals and all the early reports of vagotomy in man that I could find by searching the indexes from 1885 to date. I was aided by the fact that I was already conversant with the literature, having long been interested in the subject.

EARLY VAGOTOMIES ON ANIMALS

Most of the older reports of vagotomy in animals, written before 1900, are of little value today because so many of the experimenters cut the nerves so high in the neck or the thorax that they destroyed important fibers supplying the larynx, heart, lungs and esophagus. As a result the animals promptly died (see Frey (1)). The work of many of the later experimenters also is not very helpful because they did not observe their animals long enough, and they did not wait to see what would happen to the digestive tract and the health of the animal after sufficient time had elapsed for degeneration of the nerve endings. Another fault was that few of those men who did wait a while for degeneration of the nerve endings studied the digestive tract in action roentgenologically or with an abdominal window, or, better yet, directly, with the animal's abdomen open under a bath of warm saline solution. Only with this last technic can one measure any deviations from normal that may appear in the behavior of the stomach and bowel.

Early vagotomies in the necks of animals. The earliest workers, when their animals promptly died, concluded that vagotomy was a fatal operation, but around the first of the century, a number of physiologists kept dogs alive with a bi-vagotomy in the neck, doing it largely as a stunt.

Vagotomy and the psychic secretion. Pavlov and Schumova-Simanowskaja (2) in 1889, reported that in dogs vagotomy puts an end to the gastric secretion normally produced by sham feeding. More on the study of vagotomy in Pavlov's laboratory can be found in books by Pavlov (3) and Babkin (4, 5) and in an article by Katschkowsky (6), a discussion by Komarov (7) and a dissertation by Jürgens (8).

Bi-vagotomy and the motor function of the stomachs of animals. Interestingly, one of the best of the early reports of subdiaphragmatic bi-vagotomy in the dog is by Arthaud and Butte (9), who wrote in 1889! Their animals suffered from anorexia, vomiting, progressive loss of weight and skin troubles.

In 1906, Cannon (10), using cats and a roentgenologic technic for observing gastric motility, found that after bi-vagotomy the stomach emptied slowly. When the splanchnic nerves were cut there was but little change in gastric motility, and when both splanchnics and both vagi were cut the gastric waves were deep and powerful. After the death of the animals so operated on, the stomach was found to be strongly contracted. Cannon's studies suggested that the results of gastric denervation are somewhat different in dogs and cats.

Unger, Bettmann and Rubaschow (11) who, in 1911, performed supradiaphragmatic bi-vagotomy in dogs, learned what Dragstedt (12) learned later with man and that is that marked gastric dilatation with stasis is likely to develop if much food is given too soon after the operation.

Starck (13), Fritsch (14, 15), Rubaschow (16), Litthauer (17), Koennecke (18), Latarjet (19), McCrea (20), McCrea, McSwiney and Stopford (21, 22), Lauwers (23), Ratkóczy (24), Morin, Kofman and Dugal (25) and Hermann and associates (26) all commented on a dilated, slowly emptying, weak-waved stomach. Some remarked on vomiting, anorexia, diarrhea, skin diseases, inanition and poor health. A few mentioned stinking, mucus-laden gastric contents.

Carlson (27) found that bi-vagotomy in dogs produced a prolonged decrease in gastric tonus, with waves of normal depth but somewhat abnormal rhythm. Section of both splanchnic and both vagus nerves left the stomach markedly and permanently hypotonic.

Starck (13) stated that bi-vagotomy near the hilus of the lung need not produce stagnation in the esophagus but Gottstein (28) and others have had trouble with the esophagus.

Hughson (29), after performing subdiaphragmatic bi-vagotomy in young dogs and observing roentgenologically, noticed a more rapid gastric emptying than normal. Apparently he did not cut enough branches to get a true vagotomy effect.

Hattori (50) studied changes in the movements of the stomach of the rabbit after bi-vagotomy and noted that peristaltic activity returned to normal after some months. Morin, Kofman and Dugal (25) studied roentgenolocically the stomach of five intrathoracically bi-vagotomized dogs and found the usual marked loss of tonus, gastrectasis, weak, infrequent waves and slow emptying. These changes did not entirely disappear even after 300 days. Interestingly, Nolf (31) found that in the chicken vagotomy produces such a weak gizzard that the bird has to be fed soft food.

According to Shay, Komarov and Gruenstein (52), in rats, vagotomy produced so much motor paresis in the stomach that the animals could be kept alive only on a liquid diet containing peptones instead of protein. If given solids to eat, the rats died in a few days with the food impacted all the way back to the pharynx.

Useful reviews of the subject of vagotomy in animals were made by Hotz (33), Fritsch (14), Rubaschow (16) and Ferguson (34). Ferguson used monkeys in his experimental work. Even more complete are the reviews of Koennecke (18), Koennecke and Meyer (35), McCrea (20), McSwiney (36) and Small (37). McCrea's review is especially interesting today because it has much on the early vagotomies in man. It is remarkable to find him saying twenty-two years ago that in view of the increasing distrust surgeons were coming to feel for gastro-enterostomy, it was time to look for something better, and that this something might be denervation of the stomach.

Borchers (38, 39) started his work on vagotomy in animals at the suggestion of his chief, Professor Perthes, who hoped to use the operation for the relief of the gastrospasm that is produced by ulcers in man. Borchers first reviewed the literature and then made studies on vagotomized cats which showed that gastric motility, at first slowed, returned to normal in five days. He then produced ulcers in the vagotomized animals and was disappointed to find that these produced as much spasm as they did when made in control animals. He could not see, therefore, how vagotomy could be a good operation for patients with ulcer. In agreement with Borchers' experiments were those of Ivy (40) who, in 1920, showed with dogs that section of the vagus and splanchnic nerves did not alter that gastric hypermotility with delayed emptying which is so often seen in cases of duodenal ulcer.

About 1922, Koennecke (18) also was thinking of using vagotomy for the treatment of ulcer but after some research and a review of the literature he concluded that the evidence available at the time did not warrant his trying out the operation in the case of man. Kostlivy (41), Hosoi, Overgard, Ascanio and I (42), Best and Orator (43) and Vanzant (personal communication) all were led by their researches to have misgivings about cutting the vagi in man.

Vagotomy and gastric secretion in animals. Some of the early work done in Pavlov's laboratory on gastric secretion after vagotomy was described by Babkin (4) in 1928 and mentioned by Komarov (7). Pavlov and his students did not seem to be impressed with the lowering of acidity after bi-vagotomy and they saw no change after univagotomy. They concluded that the vagus nerves carry both stimulating and inhibiting fibers for gastric secretion. Pavlov (3) admitted that the stomach went on secreting after vagotomy, but felt that there were important deviations from normal in the composition and secretion of the juice. Rabinkova (44) had a bi-vagotomized dog with a gastric

fistula which one year after the operation still showed a continuous secretion of from 14 to 15 c.c. of acid juice an hour.

Litthauer (17) showed a lowering of acidity in a Pavlov pouch after vagotomy, and Latarjet (19) and Thompson (45) also noted subacidity. In 1929 Hartzell (46) cut the vagi transthoracically in six dogs and subdiaphragmatically in two more. Of the first six, three survived for a study lasting five months. During this time they all showed subacidity. There was no change in the cases of the two dogs which had the nerves cut around the cardia.

In 1931 Vanzant (47, 48) found three of Hartzell's (46) dogs with a transthoracic vagotomy still living in Mann's laboratory. One was in good condition but the other two were thin and sickly. On a smoother and richer diet one of them gained weight and looked better, but the other one, in spite of much care, went on downhill. All three had a good appetite. One still suffered from diarrhea. All had regained a fairly normal gastric acidity, but, curiously, the reaction to histamine was poor. Exploratory operation in the cases of two animals, and necropsy later in the case of one, showed that there was no regeneration of the nerves to explain the return of acid secretion in the stomach.

Vanzant performed vagotomy on seven more dogs and began a four year study of these, together with three of Hartzell's animals. For a while after operation the stagnating gastric contents of these dogs had a fetid odor, as in vagotomized man and contained much ropy mucus. Free acid was usually absent. Curiously, for months, a number of the dogs constantly drooled saliva. Two vomited at frequent intervals for a long time after the operation.

After some five or six months, the gastric acidity began to return to normal, and the pH eventually fell to 2.0 (within 1.0 of normal). In four of the animals the curve of acid secretion became practically normal. In seven of the ten, gastric motility was finally restored almost to its original state.

Shapiro and Berg (49, 50) and McCarthy (51), also using dogs, found that subtotal gastrectomy plus subdiaphragmatic bi-vagotomy was followed for a time by subacidity.

Wilhelmj, McCarthy and Hill (52) found in four dogs that after partial gastrectomy and bi-vagotomy there was a decrease in acid secretion greater than after partial gastrectomy alone. Histamine still worked normally. The intestinal phase of acid secretion was marked and unusually prolonged.

Vagotomy and the subsequent health of the animals operated on. As already noted, the earliest vagotomists promptly lost most of their animals, but much of their difficulty was due to the fact that they cut the nerves in the neck. Later, when the nerves were cut just above or below the diaphragm, the mortality rate was much lowered, and many animals seemed none the worse for the operation. Others, however, did not do well. They vomited, or suffered

with gastric stasis and diarrhea. In many cases the animals died if left on the usual laboratory diet, but could be kept going if given a soft diet and much care (Beazell and Ivy (53), 1936). In some the skin ulcerated and the fur looked bad. The Pavlov school felt that vagotomy interfered with the secretion not only of the stomach but of the pancreas, also with digestion and nutrition, and it often made the animal sickly (Komarov (7) 1946).

About half of the rabbits operated on by Hosoi, Overgard, Ascanio and me (42) died of diarrhea and inanition. Katschkowsky (6) concluded that the bi-vagotomized dog often has so vulnerable a digestive tract that any little infection or a poor diet can easily start up diarrhea and send the animal into a decline. Komarov (1946) (see also Shay, Komarov and Gruenstein (32)) were impressed by the fact that their 142 vagotomized rats soon died if not kept on a liquid diet, and others noted that in vagotomized rabbits gastric ulcers tend to develop if the animals are not well cared for. Krehl (54) and Vanzant (55) commented on the fact that even with the best of care a few vagotomized dogs will get thin and sickly. Similar observations were made by Arthaud and Butte (9) in 1889!

Effects of cutting one vagus or parts of the vagi in animals. The impression gained today from many experiences with animals and men is that the cutting of only one vagus or even most of the branches of both vagi is likely to be without much if any result. As is well known today, the vagi break up on the esophagus to form a plexus, and during operations even in the thorax, some of the fibers can easily be missed. It is so difficult to cut all the fibers as they spread out below the diaphragm that all subdiaphragmatic vagotomies, in which the esophagus is not loosened up and pulled down, are suspected of being incomplete.

Interestingly, according to Morin, Kofman and Dugal (25), Brachet, in 1825, had already seen that the big problem in performing vagotomy below the diaphragm was to get all the fibers. Later some surgeons, after cutting all visible branches, cut through the gastric muscle around the cardia, down to the mucosa and turned in the edges, and still the stomach did not behave as a completely vagotomized stomach should behave. One of the first to "circumcise" the stomach was Stierlin (56) in 1920.

In view of the present-day troubles of surgeons in attempting to get all branches of the vagus and in puzzling over whether a given vagotomy is complete, it is interesting to find Krehl (54), in 1892, struggling with the problem. He could not see why some experimenters who cut both vagi in the thorax got so much gastric stasis that they could hardly keep their dogs alive, while others who cut every fiber they could find below the diaphragm saw no change in their animals. As he said, it would seem that a few fibers must have been left, but

"it is most remarkable that a thin little branch can so perfectly take over all the functions of the two big nerves!" No one could better summarize the problem today.

Friedenwald and Feldman (57) cut one vagus nerve in dogs and found a little lowering of acidity in some of them. Later, Friedenwald, Feldman, Morrison and Ullman (58) made a careful study of dogs most of which had only one vagus cut, and found no definite change from normal. More on the subject will be found herein under the heading of "The cutting of one vagus in man."

The transabdominal approach to the lower end of the esophagus. In view of Moore's (59) discovery in 1946 that the easiest way of getting at the lower few centimeters of the esophagus is to go through the abdomen, loosen up the hiatus and pull down the stomach, it is interesting to note that this or a similar operation was used on dogs by Krehl (54) in 1892, by Frouin and Pozerski (60) in 1904, by my associates and me (42) on rabbits in 1929, and by Lasowsky and Ptschelina (61) on dogs in 1932. Particularly interesting is the fact that this technic was used by Exner (62, 63) in his first bi-vagotomy on man in 1911. It apparently was used by Pieri (64) in 1930.

The fear of immediate death due to vagotomy in man. Partly because of early bad results with high vagotomies in animals and partly because of a few cases of sudden collapse and even death in man on cutting a vagus nerve spread out over a tumor in the neck, the early surgeons feared vagotomy.

Actually, it was early learned in the laboratory by Hotz (33), Pavlov (3) and others that there is usually no immediate reaction to the cutting or stimulation of the vagi near the diaphragm; there is no effect on respiration or the heart action.

Using rabbits, Mahoney and I, around 1924, often cut the vagi while records were being made of the intestinal activity in a half-dozen places, and we could see no change in either the contractions or the level of tonus of the muscle. On a few occasions, however, my associates and I (42) saw shock develop in an animal and for this reason we often blocked the nerves with procaine before cutting them, just as Moore and associates (65) did in the case of men and women.

Widmer (66), Giordano (67), Martini (68), Reich (69) and Zesas (70) searched the literature for reports of the results of injury to the vagus nerve or the accidental cutting of one nerve or both during an operation. The need for such information was felt acutely by German surgeons when Sauerbruch's invention enabled them to enter the thorax and attempt the removal of cancers of the esophagus. A few records were found of cases in which, for a while after vagotomy, usually carried out high up in the neck or thorax, there was tachycardia or a sudden disturbance in respiration due, perhaps, to undue stimulation of the nerve (Reich, (69) pp. 702 and 703). There were reports of a few persons

who died suddenly, but in their cases there appeared to be extra handicaps to life. Thus, in the case of Roux (71), the man stopped breathing and died when a ligature was put on the left vagus nerve in the neck. The man had a parotid carcinoma with metastasis. There was the case of Faure (72) in which the woman expired when he picked up the left vagus nerve. One reason may have been that the patient had long suffered from a toxic goiter and the other that she had just had her cervical sympathetic nerves cut.

Reich (69, p. 735) found records of fifteen cases in which trauma to a vagus nerve had caused sudden severe disturbance with the respiration. In Michaux' (73) case, when he put a ligature on a vagus nerve, the patient cried out, stopped breathing and lost consciousness. Fortunately, when the ligature was removed the patient recovered.

Voelcker (74) found that he could perform intrathoracic bi-vagotomy in man without difficulty, but he warned against traumatizing the nerve. In a case of retropharyngeal sarcoma with one vagus spread out over the capsule, efforts to free the tumor caused the patient to collapse and die with Cheyne-Stokes breathing. A similar case of sudden great distress in which the man almost died, was reported by Tuffier (75). That there still is some immediate danger in vagotomy was shown by Weeks, Ryan and Van Hoy (76) who had a patient die suddenly as one of the nerves was cut.

Moore and his associates (65), forty-eight hours after operation, had a death which they thought might have been due to vago-vagal reflexes. After that they made it a rule to cocainize the vagi before cutting them.

Recently, while operating on men and women under local anesthesia, Dragstedt, Grimson and others have noted, as did the earlier workers, that the cutting of the vagi is not felt, and usually produces no disturbance. Even electrical stimulation of the central ends of the cut nerves has produced nausea and vomiting, but not pain (Foerster (77)). More on this subject will be found herein under the heading of "Does the vagotomy desensitize the stomach?"

THE CUTTING OF ONE VAGUS IN MAN

Some of the earlier studients of vagotomy in man dared only to cut one of the nerves. Others cut the nerves here and there so far below the cardia that it is doubtful if they could have gotten a physiologic result.

Giordano (67) in 1893 collected reports of many cases in which one or both vagus nerves were injured or cut during operation on a tumor in the neck. In 1893, Widmer (66, 78) wrote on univagotomy in man.

Bircher (79) did a poor type of subdiaphragmatic vagotomy in twenty cases of ulcer or ptosis of the stomach and reported such uniformly good results that one must suspect that he did not cut enough fibers to get some of the now well-known temporarily distressing effects of vagotomy.

In 1920 Stierlin (56) remarked that for years physicians had known that the patient with ulcer usually has a peculiar nervous system and that flare-ups commonly follow psychic strains. He said this fact had been impressed on him on countless occasions during the first World War. He apparently performed some vagotomies, but his report is so vague that it is hard to know what he did. Steinthal (80) said he tried Stierlin's operation in two cases but went no further with it, because he obtained no change in either gastric peristalsis or secretion.

In 1924 Thomsen (81), after doing work on dogs which showed him that by vagotomy he could produce an achylia which would last a few weeks, got Schaldemose to cut the left vagus in the case of a young man with severe gastric crises. According to Thomsen, the cure was prompt.

In 1922 Latarjet (19), reported twenty-four probably incomplete subdiaphragmatic vagotomies, six of them for ulcer. He felt encouraged with his results, but soon concluded that vagotomy should be performed only as a complement to gastro-enterostomy. He hoped the new operation would be helpful in cases of nervous indigestion.

In 1923, Gianolla (82) performed eight vagotomies of the Latarjet type, usually in addition to gastro-enterostomy or partial resection. He saw some good results, but could not be sure that they were due to the denervation. He said Wertheimer had seen his chief perform twenty-three vagotomies, and that he, Gianolla, had seen Pauchet perform several.

In 1923 Latarjet and Wertheimer (83) reported twelve vagotomies which were probably incomplete, and were done mainly on neurotic chronic complainers. In eleven the results appeared to be good, at least for a short time after the operation.

In 1923 Göbell (84), with the hope of curing asthma, followed Kummell's suggestion and began to cut one vagus nerve below the recurrent branch in addition to resecting the cervical sympathetic nerves on both sides. In 1928 (84) and 1933 (85) he reported 112 cases, with encouraging results in some. In 1924 Kappis (86), also trying to cure asthma, cut the right vagus below the recurrent branch. Schittenhelm and Bruning (Foerster (77), 1927, p. 255) also did some of these operations. Kern (87), in 1926, reviewed the literature on this method of treating asthma. He operated on one patient, cutting the left vagus, but saw no improvement.

Kostlivy (41), in 1925, reported permanent relief of painful gastric spasms in a few persons after univagotomy.

In 1925 Schiassi (88), tried to denervate only the pars pylorica and the duodenal cap, with or without gastro-enterostomy. He reported twenty-three operations but did not say much about the results. Dr. Charles H. Mayo also tried a few such operations.

Barron, Curtis and Haverfield (89) and Barron and Curtis (90) cut the left vagus in man and observed a surprising speed-up in gastric motility. Bircher (91), in 1931, stated that in 1912 he had cut the left vagus and cured constant vomiting following gastro-enterostomy. He stated that in 1918 he reported some cases of "vagus fiber resection."

Pieri and Lapenna (92) cut the left vagus nerve above the diaphragm in eight patients, and then made a roentgenologic study of gastric motility. Unfortunately they do not appear to have made a preoperative control study. They observed in several of the patients a hypotonic gastric wall, sometimes weak or "incoordinated" activity, and sometimes slowed gastric emptying. These abnormalities tended to clear away in a few weeks or months.

For several years, at Mount Sinai Hospital in New York, the gastric surgeons studied the effects of cutting one vagus nerve in addition to performing gastro-enterostomy or subtotal gastrectomy. The results were not decisive enough, and unfortunately the univagotomy did not protect the patient from the later formation of a jejunal ulcer. Klein (93), Winkelstein (94), and Winkelstein and Berg (95) were encouraged for a time about the operation because the vagotomy appeared to increase the incidence of anacidity. Weinstein, Colp and associates (96) reported their experience with six cases of partial vagotomy which showed that this operation is not sufficient to produce definite physiologic or therapeutic results. De Takats (97) also reported that his subdiaphragmatic vagotomies on man between 1936 and 1939 were probably incomplete, as they produced no lasting effect.

Today everyone seems to agree that the cutting of one vagus or even one vagus and parts of the other is likely to be without therapeutic or physiologic effect. There is much doubt about the efficacy of any vagotomy done below the cardia because of the likelihood that it is incomplete.

Watanabe (98) discussed the problem of whether, after vagotomy, splanchnicotomy would make matters better or worse. He gave a summary of some of the literature which indicated that it does not help to add splanchnicotomy to vagotomy.

EARLY EXPERIENCES WITH BI-VAGOTOMY IN MAN

According to McCrea (20), the first surgeon to suggest gastric denervation in man was Jaboulay, in 1899. He, however, proposed to do this by extirpating the celiac plexus. As McCrea noted, a number of the first surgeons to operate on the vagus nerves were remarkably vague as to their results, except to say that "they were excellent." Often the patient was not well studied before or after the operation and sometimes the operation was done for a neurosis or ptosis!

It would appear that shortly before 1907, there had been some flurry of in-

terest in bi-vagotomy because at that time one finds Tuffier (75) advising his fellow-surgeons to go easy with it. He said he had performed several vagotomies without accident, but then he had a bad scare with two patients. In one case, that of a physician, operated on without anesthesia, he opened a phlegmon of the neck. The moment he touched tissues close to a vagus nerve the patient felt great anguish, his heart almost stopped, and he felt he was dying. Fortunately, after a while he recovered. In the other case in which he resected one vagus in the neck where it was spread out over the surface of an aneurysm in a woman, rales promptly developed in the homolateral lung and soon pneumonia with abscess formation occurred. The other lung remained normal.

Tiegel (99) studied bi-vagotomy in the thorax of man incidental to resection of carcinomas of the esophagus, and found it could usually be done without serious result. Fritsch (15) agreed with this, but he (14) was a bit fearful, partly because of the stasis he had seen in the stomachs of bi-vagotomized dogs and partly because of stasis he had seen in the stomachs of patients so operated on. To avoid such stasis he warned surgeons that while cutting the nerves they had better also perform gastrostomy. This was in 1910.

Perhaps the clearest of the early records of bi-vagotomy in man is that of Exner (62, 63) who, in 1911, reported two cases at the surgical congress at Berlin. He operated with the hope of relieving the gastric crises of tabes. Most interesting is the fact, already noted, that at his first operation he found he could loosen up the cardia and pull down 3 cm. of intrathoracic esophagus so as to make certain that he would cut all of the vagus fibers! Then he sewed the diaphragm back around the cardia and performed gastrostomy so as to have a safety valve. Perhaps he had been warned by Fritsch (14, 15) that such an extra operation would be advisable. Unfortunately, in Exner's second case there was leakage about the stoma and the patient died because of a subphrenic abscess. The other patient recovered and for a while suffered from some gastric and esophageal stasis.

In 1912 Exner and Schwartzman (100) reported three cases of bi-vagotomy, but said nothing about the results except that sometimes months later there still was "pylorospasm." Two years later they (101) reported fourteen cases in all. One patient died a few months after operation, from endocarditis, and another committed suicide. A few were relieved of pain. Not all of them showed a lowering of gastric acidity. Küttner (102) later tried an Exner vagotomy for gastric crises, but the patient was the worse for it. In 1913 he (103) cut both vagus roots as they left the medulla, and the patient did not feel any shock. Interesting is Borchers' (38) comment that the crises came back, and hence this operation could have no place in the treatment of tabes. Foerster (77, pp. 70 and 291) performed a number of Exner vagotomies without good results.

Podkaminsky (104) stated that vagotomy of the Exner type seemed indicated in some cases; that it would make a flabby, slowly-emptying stomach and might cut down some on gastric secretion, but he did not report any operations. It is helpful to note that Borchers, who wrote in 1921 and evidently was thoroughly conversant with all that was going on surgically in Germany, wrote that so far as he knew only Exner and his co-workers had tried bi-vagotomy.

Bircher (79), however, in 1920, reported twenty cases in which he had cut the anterior and posterior branches of the vagi mainly with the idea of curing gastric ptosis! Judging from his reports, he never obtained typical vagotomy effects as we know them now. Later, in 1931, Bircher (91) stated that Loeper, Marshall, Houkgeest and Wertheimer had performed vagotomies, apparently in man, and had gotten an atonic, dilated stomach that emptied slowly and had a lowered acidity. Bircher said that up to 1919 he had cut both vagi below the diaphragm in twenty cases, with good results in 75 per cent. The acidity was usually reduced, but, curiously, he thought the gastric wall had an improved tonus. In the years from 1921 to 1931 he performed some 150 such subdiaphragmatic operations, often with the hope of curing functional disturbances of various kinds. Occasionally, he performed at the same time gastro-enterostomy or some operation designed to relieve ptosis. His vagotomies were probably incomplete because, aside from some lowering of acidity, he did not seem to obtain the usual effects of a complete nerve section.

In a discussion that followed Bircher's paper, Haumann (105) reported having done some bi-vagotomies which resulted in a lowering of gastric acidity.

In the years from 1927 to 1930 Pieri, (92, 106) and Pieri and Tanferna (107) reported a few vagotomies in man, with favorable results. For a while acid disappeared from the stomach, but later it returned. The tone of the stomach, at first lost, was eventually regained. In 1932 Pieri (108) reported fourteen bi-vagotomies without untoward results.

On reading through some of the discussions that took place at surgical congresses one finds evidence indicating that around 1914, 1924 and 1930 a number of surgeons were performing vagotomy just as surgeons are doing today and not writing up their experiences.

The era ushered in by Dragstedt. As everyone now knows, in 1943 Dragstedt and Owens (109) ushered in an era in therapeutics when they reported their results with vagotomy in two persons with duodenal ulcer. Both of the patients were promptly relieved of their distress, and the quantity of the night secretion of gastric juice was found to be greatly reduced.

In 1944 Dragstedt, Palmer, Schafer and Hodges (110) reported eleven operations. In some patients the sensation of hunger was lessened; in two there was some dysphagia for two weeks, but no cardiospasm and no gastric reten-

tion, if it had not been present before operation. Two patients required gastro-enterostomy.

In 1945 Dragstedt and Schafer (111) reported thirteen vagotomies. Three patients required gastro-enterostomy because of the persistence of obstructive symptoms, and one of the patients with duodenal ulcer and one with a jejunal ulcer were not cured.

Storer, Thornton and Dragstedt (112), using the balloon technic in seven patients with ulcer, found, before vagotomy, hypertonicity and hypermotility. Following the operation, gastric tonus and gastric motility were decreased. Curiously, in one patient with a flabby, obstructed and dilated stomach before operation the motility was improved after vagotomy. Vagotomized patients still felt hunger and appetite, and they could eat more with less sensation of distention.

Thornton, Storer and Dragstedt (113, 114) found that after vagotomy gastric acidity varied from 0 to 61 units. The acid-forming cells still responded well to histamine and caffeine. Sham feeding, which caused some secretion in three of ten patients before operation, had no effect after operation. More details as to the workings of vagotomy are to be found in articles by Dragstedt, Woodward, Harper and Storer (115), and by Dragstedt, Palmer, Schafer and Hodges (110).

Moore (59, 65) found no change in the total base or pepsin concentrations in the gastric juice.

Grimson and associates (116) reported the results of eighteen transthoracic bi-vagotomies. Seventeen of the patients soon returned to full activity, but one, a neurotic person, got a bad diarrhea and lost much weight. The others gained weight. Five had to undergo gastro-enterostomy and three were subjected to pyloroplasty. Right after the operation two patients suffered acute dilatation of the stomach. Walters (117) had three cases of severe gastrointestinal atony after operation, and Chester Jones (118) saw an acute dilatation of the stomach that lasted five days.

Sanders (119) reported fifty cases, with good results in 94 per cent.

THE COMMONER RESULTS OF VAGOTOMY IN MAN AS KNOWN TODAY

Today certain results of complete bi-vagotomy in man are well known. Usually, there is a prompt relief of ulcer distress, with a more or less marked lowering of gastric acidity and a lessening of the amount and acidity of the night secretions. Griswold (120) reported that in his cases the average volume of twelve-hour night secretion before operation was 1,300 c.c. and after vagotomy, 270 c.c. Usually, for a time, there is atony of the gastric wall, with shallow irregular contractions and a marked delay in gastric emptying.

The gastric stasis probably accounts for the fact that most of the patients

complain for a while of feeling too full. In some there are frequent foul-smelling eructations. Quite a few patients are for a while troubled by diarrhea, and in a few this remains for months. A number of the patients are for a time left feeling very weak, so they cannot work, or cannot work all day.

In about half of Grimson's cases there was dysphagia, perhaps with cramps in the esophagus. In a few cases this lasted for months. A few of Grimson's patients were much troubled by vomiting and one kept it up for months, in spite of the performance of gastro-enterostomy.

In Grimson's (121) series there was an average loss of weight, after operation, of 24 pounds (10.9 kg.), but all but six of his fifty-seven patients soon regained this. Some 40 per cent suffered for a time with diarrhea, and in a few this became chronic. In most cases any pre-existing constipation was relieved by the operation.

Some of the patients continued to suffer from curious episodes of intense, colicky abdominal pain which caused six of them to return to the hospital for a while. With this pain there were nausea, vomiting and some distention of the abdomen. In four of the patients the syndrome was so alarming that, for a time, it was thought that the abdomen would have to be reopened. The mechanism of this pain is not known. In one patient it kept recurring for ten months, in another for eighteen months, and in another, for twenty months. One man remained in such pain that eleven months after vagotomy his abdomen was explored surgically; an active duodenal ulcer was then found.

Surgeons have reported occasional cases of what looked like paralytic ileus soon after the operation, and in some cases the situation was so alarming that the patient's abdomen was explored surgically.

Thirty-one of Grimson's patients were bothered for months with excessive flatus, and some were annoyed by abdominal rumblings. Twenty-three of the first ones operated on, who submitted to vagotomy alone, suffered much from gastric stasis and five later had to submit to gastro-enterostomy.

In one of Bockus' (122) cases the man's stomach was still unable to empty itself nine months after the operation. At all times this stomach was full of a viscid, foul-smelling mass of mucus and food. That vagotomy need not produce subacidity was shown by this case of Bockus. The man had a free acidity of 90 units! Already evidence is coming in to indicate that, just as in dogs, so in man: after a while much of the ability of the stomach to secrete acid returns. In many of these cases Moore and associates (123) found secretion back to normal in from six months to a year. The motility came back in from nine to twelve months.

Why vagotomy so promptly relieves the distress of peptic ulcer. There are a number of questions that have been arising in the minds of physicians and surgeons since the reports began to come in about the results of vagotomy.

One question is: when, as usually happens, the operation promptly relieves the distress of ulcer, how does it do it?

The prompt relief of the pain of ulcer after vagotomy may well be due to the loss of tone and activity in the stomach (see Ruffin and associates (124), 1946). This was suggested by the fact that in some patients the restoration of gastric tone by the taking of urecholine brought back the pain. That it is not necessarily due to a loss of acidity was shown when four of Grimson's patients who had achlorhydria to begin with lost their pain right after vagotomy. More proof of the fact that the production of subacidity is not the whole secret was given by the reports of some cases in which a good result was obtained in spite of the fact that the operation did not lower gastric acidity.

Perhaps the greatest light on the mechanism which causes vagotomy to cure ulcer was thrown by some observations made by William D. Andrus and reported in the discussion on the paper by Moore, Chapman, Shulz and Jones (123). A man had a gastrostomy through which the condition of the gastric mucosa could be observed. Before vagotomy, anger and resentment would produce the typical vascular response described by Wolf and Wolff (125), with marked reddening of the mucosa; after vagotomy, painful emotion strong enough to bring a flush to his face no longer affected the gastric mucosa. Moore and associates (1947, p. 746) also commented on the fact that a patient of theirs who, before the vagotomy had a flare-up of his ulcer every time he got all upset, after the operation did not so respond to emotion.

Does the vagotomy desensitize the stomach? One question that has bothered many physicians is: Does vagotomy leave the stomach so anesthetic that the perforation of an ulcer might not be felt? Probably not. It has been known for years that although there are a few afferent fibers in the vagus bundles, they are of use mainly for mediating reflexes and are usually not able to transmit pain. Foerster (77, p. 35) noted repeatedly in soldiers with the spinal cord transected above the sixth thoracic segment, above the entrance of sensory nerves from the abdomen, that strong pressure in the epigastrium might cause nausea but not pain. Pain sensations from the digestive tract go out to the spinal cord and brain by way of the splanchnic bundles (see Preiss (126); Foerster (77); Balchum and Weaver (127)); pain arising in the parietal peritoneum goes out by way of spinal nerves.

One of the best proofs that the vagi do not ordinarily carry pain-transmitting fibers was obtained by Foerster (77, p. 34) when, in the cases of persons being vagotomized under local anesthesia, he stimulated electrically the central ends of the vagi. The persons became nauseated but did not feel pain.

That the vagi carry afferent messages which can be felt as pain in the sensory area of this nerve around the ear has been shown by some of my patients when they had an acute ulcer or a gastric hemorrhage. Foerster (1927, p. 296)

also knew patients who before a gastric crisis would get pain in the skin distribution of the vagus nerves.

A way in which to show that vagotomy does not desensitize the esophagus, stomach or bowel is to blow up a balloon in these tubular organs before and after the operation and thus to see if the threshold pressure that will produce pain has changed. This was done by Moore (65, 123), and no change was found. Some physicians have run 200 cc. of a 0.5 per cent solution of hydrochloric acid into the stomach through a tube shortly after operation and before the ulcer could have healed much, and the patient felt it as he had before the operation.

Indicative also of normal gastric sensitivity is the fact that after vagotomy patients can feel full after a meal. In many cases persistent or new ulcers have produced pain as usual, in spite of vagotomy.

Curiously, however, in spite of the fact that vagotomy does not anesthetize the stomach or bowel, there have been a few cases in which some time after the operation an ulcer has perforated without producing the usual paralyzing pain. In one case Walters and associates (128, 129) were surprised at necropsy, two weeks after operation, to find a postperforation abscess.

Much of the literature on what afferent fibers there are in the vagi can be reached through the review of Goldberg (130), and through articles by Adrian (131), Meek and Herrin (132), Harper, McSwiney and Suffolk (133), McSwiney (134), Balchum and Weaver (127) and Herrin and Meek (135).

In 1932 Holinger, Kelley and Ivy (136) made a remarkable observation in a dog with complete anorexia after the production of a pouch of the whole stomach and jejunal fistula for feeding. For months the animal refused to take food by mouth. Then both vagi were cut and immediately, on recovery from the anesthetic, the animal started to wolf down all the food he could get. It would appear that the anorexia was due to some gastro-intestinal disturbance which was sending messages of disgust for food to the brain along the vagi.

That ulcers can bleed badly without pain after splanchnicotomy was noted in three cases by Moore (123). Moore emphasized the fact that vagotomy must not be performed in an attempt to relieve abdominal pain not due to peptic ulcer.

Is the insulin test always trustworthy? As every gastric surgeon knows today, when vagotomy is done and especially if the patient does not promptly get well, the questions arise: Were all the fibers cut? and, what would an insulin test show?

In 1924 Bulatao and Carlson (137, 138) showed that insulin will increase the activity of the gastric, duodenal and colonic muscle and this was confirmed by Quigley, Johnson and Solomon (139), Quigley and Solomon (140) and Quigley and Templeton (141). Quigley and Solomon (140) showed that this action

was altered by vagotomy, and they suggested that it might be used as a test for the intactness of the vagi.

In 1925, Detre and Sivó (142) showed that insulin in large doses usually increases the acidity of the gastric juice. This was confirmed two years later by Wiechmann and Gatzweiler (143), who recognized the fact that the vagi had to do with the effect. In 1929 Okada and associates (144) showed this clearly in man and showed that the hypersecretion was due to hypoglycemia. In 1930 and 1931 Okada and associates (145), Roholm (146), and La Barre and de Cespédès (147–150) all showed that the insulin effect on gastric juice could be blocked by vagotomy. Incidentally, Okada (144–145) showed that the injection of large amounts of amino acids would provoke a similar hypersecretion in the stomach which could be blocked by vagotomy.

In 1938 Babkin (151) reviewed the literature on this test, and later Jemerin, Hollander and Weinstein (152) and Hollander (153) performed a great service by calling the attention of surgeons to the test. In this test a negative reaction with a failure to stimulate gastric acidity means that the fibers were all cut, while a positive reaction suggests that many were left intact.

Actually, evidence is now accumulating which has shaken the confidence of many surgeons in the test. The trouble is that a patient who appears from the test to have had all his vagal branches cut may not show the triad of gastric stasis, subacidity and relief from pain, while one whose test indicates that the nerves were not all cut may show a good triad. In Walters' (128) experience the percentage of good results was decidedly higher in the patients with a positive reaction than in those with a negative reaction, which is just the reverse of what one would expect. Disturbances of motility occurred as often with a positive as with a negative reaction to the test, and a big reduction of acidity occurred in 69 per cent of cases with a negative reaction and in 93 per cent of cases with a positive reaction! Colp (154), Moore and associates (123), and Collin and Stevenson (155) were all puzzled by instances of this type of inconsistency. Moore (123) reported (p. 745) that repeated tests on the same patient have given different results. Necheles (156) found the insulin test at times misleading, and stated that if the blood sugar level drops too fast or too far other mechanisms may come into play that will abolish the stimulating effect or will inhibit secretion.

Perhaps in some cases the positive results are correct and some vagal fibers have been left, but not enough to maintain the normal tonus and acidity in the stomach and not enough to interfere with the cure of the ulcer. Another possibility can be seen from the work of Moore and his associates (1947) and Levin, Kirsner and Palmer (157), who found considerable individual variability in the reaction of the gastric cells to hypoglycemia, before vagotomy. This suggests that after vagotomy the patient with a normally weak response might show

no response after an incomplete section of the nerves. This view is strengthened by the observation that in some cases a negative insulin reaction has later changed to a positive one.

Some physicians have suggested also that Iwama (158), Kiss (159), Rasmussen and Duncan (160), Duncan (161) and others are right in suspecting that some vagus fibers cross over in the neck and go to the stomach by way of the sympathetic nerves. Against their ideas was the work of McSwiney and Spurrell (162).

Only future experience with the insulin test will give an answer to the puzzle that we have today.

Does vagotomy in some way protect from the formation of ulcers? Naturally, the question has arisen: Is there something about vagotomy which protects the gastro-intestinal mucosa from the formation of ulcers? The answer so far appears to be, "No." In man, gastric and jejunal ulcers have been observed to form shortly after vagotomy. In 1929 Bürkle-de la Camp (163) found that bi-vagotomy did not protect rats from the production of gastric ulcers due to the giving of histamine.

Dragstedt and Ellis (164), who prepared total isolated stomachs in dogs, preserving the vagal innervation, found that such total pouches secreted excessively and in some there developed ulcers. In contrast, Ivy (40) found that such stomachs, when freed from vagal influence, did not secrete to excess and that ulcers never developed in them. None were found in 100 experiments.

Beaver and Mann (165) showed that vagotomy does not always protect dogs from the development of a Mann-Williamson ulcer. It may have done so in one case. Harkins and Hooker (166) thought that it did protect but Saltzstein and his associates (167) and Oliver (168) had to conclude that vagotomy increases the incidence of Mann-Williamson ulcers. Vagotomy was effective in protecting animals against the acute type of ulcer that comes when the pylorus is tied off. In the cases of eight dogs in which Shapiro and Berg (50) had performed partial gastrectomy, subdiaphragmatic bi-vagotomy did not ward off jejunal ulcer in two.

Baronofsky and associates (169) found that in dogs, cats and rabbits, vagotomy did not protect against the formation of ulcers by chronic histaminic stimulation. Perhaps there was not much reason to suspect that it would. One would think that vagotomy should protect mainly against ulcers that are to be produced by impulses coming down from the brain. Against this idea is the finding of Keller and D'Amour (170) and Keller (171) that vagotomy in dogs does not protect the digestive tract from the formation of those hemorrhagic states which follow hypophysectomy or the making of lesions about the optic chiasm.

Can vagotomy produce peptic ulcers? Another question that arises is: Is

vagotomy likely to produce ulcers? The answer is, "Yes." There is a large literature on the production of chronic gastric ulcers by vagotomy. Zironi (172) reviewed a large part of it and reported many of his experiments on rabbits in which he produced ulcers. Antonini (173) also reviewed the literature, and then cut the vagi in forty rabbits and ten dogs. He found gastric ulcers in about 7 per cent of the animals. My associates and I (42) saw ulcers in a number of vagotomized rabbits. Beazell and Ivy (53) found that in 66 per cent of vagotomized rabbits subsisting on a rough diet gastric ulcers developed. On a smoother diet the incidence was about 15 per cent. Unger, Bettmann and Rubaschow (11) cut both vagi in dogs and caused some chronic ulcers. Keller (171) found that thoracic bi-vagotomy in dogs produced acute and chronic gastric ulcers *only* when the dogs were allowed out in the yard in winter (in Alabama).

THE EFFECTS OF VAGOTOMY ON THE BOWEL

Surgeons have been wondering why some vagotomized patients have so much trouble with diarrhea. The best explanation available appears to be that of Alvarez, Hosoi, Overgard and Ascanio (42) who, after bi-vagotomy in rabbits, found an overly active bowel with abnormally frequent peristaltic rushes. We opened the animals' abdomen under a bath of warm saline solution and could see that the least stimulus, such as picking up a segment of bowel, would cause it to contract powerfully into a white cord. Often, then, a peristaltic rush would start from this stimulated place. Perhaps because of this great irritability, in about half of the rabbits the colon and cecum promptly emptied out and the animal got a diarrhea which often seemed to be responsible for its death.

My associates and I noted an even greater irritability of the bowel following splanchnicotomy, and this was observed also by Cannon (10), Koennecke (18) Koennecke and Meyer (35) and others. A still greater irritability and mortality followed excision of the celiac ganglia. Only with difficulty could Lamanski (174), Ivy (40), Koennecke (18), Koennecke and Meyer (35), and Olivecrona (175) keep alive a few of the animals so operated on.

Hosoi, Overgard, Ascanio and I (42) found evidence that after vagotomy some of the nervous conducting paths in the small bowel are destroyed. This was indicated also by the work of Thomas (176) and Thomas and Morgan (177), who found that vagotomy interfered with the "entero-gastric reflex" which causes the stomach to become inhibited when a Thiry fistula segment is distended.

Much of the evidence available indicates that both the vagi and the splanchnics serve as brakes to keep the bowel from being too irritable and responsive to every stimulus.

It is possible, of course, that changes in absorption and secretion in the small bowel contribute to the production of the diarrhea. Saltzstein and his associates (1947) found jejunitis in 60 per cent of vagotomized Mann-Williamson dogs and thought this might be a cause of diarrhea. Walters (178) saw signs of jejunitis in some of his cases.

Curiously, Cannon (10), using cats and observing with the roentgen rays, found the passage of food through the small bowel slower than normal after vagotomy. After section of the splanchnic nerves, the passage was accelerated. With all of the nerves cut, the rate of passage was slower than normal.

Koennecke (18) and Nolf (179, p. 464) could not see that vagotomy had much effect on the bowel. According to Nolf (1929) the progress of waves in the small bowel of the chicken was slowed. Drake and associates (180) cut both vagi and splanchnics in rabbits and rats and allowed time for degeneration. They then found no change in the response of the bowel to a number of drugs. Youmans, Karstens and Aumann (181) found that vagotomy has little if any effect on the sensitivity of the jejunal muscle to epinephrine.

It is doubtful if in most animals and man the vagi have any direct influence on the colon. They do not seem to reach that far. (For the literature, see Alvarez (182) pp. 246 and 506.) They might have an influence, however, in preventing those common effects of fear on the bowel which lead to the production of diarrhea. Perhaps this is the explanation for the good results of vagotomy in cases of chronic ulcerative colitis reported by Dennis and Eddy (183). They observed no difference in the transit time of food residues through the bowel after vagotomy. Walters and associates (117, 128) reported that in some of their cases operation was followed by the appearance of low-grade obstruction in the jejunum.

WILL VAGOTOMY INJURE TROPHICALLY THE STOMACH, LIVER, PANCREAS, OTHER ORGANS OR BLOOD?

Before vagotomy can be accepted as a safe procedure, the medical profession must have at its disposal detailed necropsy reports concerning patients who died several years after the operation. As yet what little evidence there is suggests that vagotomy does not bring serious changes in the functions or histology of the several abdominal organs.

The stomach. Martini (68, p. 6) after vagotomy studied histologically the heart, lungs, stomach, liver and kidneys and could not see any abnormality. He discussed the literature then available. Jennings and Florey (184) showed that the vagi have much to do with the secretion of the mucus-forming cells of the stomach and duodenum. Lasowsky and Ptschelina (60) made a histologic study of the gastric mucosa about a week after bi-vagotomy in dogs, and found little beside an increase in the formation of mucus.

The liver. Arthaud and Butte (9) (1889), who cut both vagi in dogs, reported that at necropsy they found the liver depleted of glycogen. There were congestive changes in the stomach, liver and kidney. Shay, Komarov and Gruenstein (32), using rats, saw no difference in the absorption of fat and glycogen by the liver. In rabbits, Matsumoto (185, 186) found little histologic change in the liver if he had given a normal diet. If he had fed much lanolin, there was a greater than normal tendency toward the production of cirrhosis. Vagotomy disturbed the pigment-excreting function of the liver.

Tanturi and Ivy (187) found in the vagi afferent and efferent fibers which influence the secretion of bile. Boyden and Van Buskirk (188) concluded that in the cat the cutting of the right vagus nerve removes fibers which activate the gallbladder and some which relax the sphincter of Oddi. Curiously, the cutting of both vagi had no retarding effect on the rate of emptying of the gallbladder.

Moore and associates (123) and Snape (189, 190) found no change in the functions of the gallbladder after vagotomy.

The pancreas. Pavlov (3) thought that the vagi were the secretory nerves of the pancreas, and the effects of these nerves on the external secretion were discussed by Babkin (4).

Levene (191) found that although stimulation of the vagi increases sugar production in the liver, the cutting of the nerves does not cause a lowering of the blood sugar in the body. Nakayama (192) found in rabbits a decided lowering of blood sugar after vagotomy, but could not explain it. Clark (193–195) collected evidence suggesting that the vagi have a little effect on the islets of Langerhans. He reviewed the literature. Quigley, Hallaran and Barnes (196) found that in dogs vagotomy does not lessen the sensitiveness of the islet response to hyperglycemia.

Högler (197) and Högler and Zell (198) concluded from their extensive experiments on rabbits that the vagi have little to do with the islets.

Gley (199) concluded from some work by Coro that vagotomy does not interfere with the formation of secretin in the wall of the bowel. Rasenkow (200) (1929) concluded that after vagotomy there are trophic changes in the cells of the pancreas and changes in the activity of the gland in response to secretin. Crider and Thomas (201) found after bi-vagotomy in dogs that there was a temporary absence of the pancreatic secretion in response to the injection of peptone into the bowel. There was no diminution of the response to soap in the bowel.

Blood chemistry. Cokkalis and Nissen (202) described changes in blood chemistry after vagotomy, associated with changes in the gas exchange in the lungs. Conceivably, such changes might go with some of the marked flatulence complained of by some patients after vagotomy.

Friedenwald, Feldman, Morrison and Ullman (58) performed univagotomy in dogs and found no consistent change in blood chemistry.

Blood pressure. Reed (203) saw little immediate effect on blood pressure after vagotomy in dogs. Reed and Layman (204) found some lowering of blood pressure immediately after vagotomy, due to removal of the path by which tonic impulses reach the vasomotor centers. This matter was discussed at length also by Thompson and Dick (205)).

Raymond-Hamet (206) reviewed the literature on the immediate effects of high vagotomy on the circulation, and performed some experiments on dogs. He found that the blood pressure rises for a few moments after the second vagus is cut in the neck.

CONCLUSIONS

It appears that in many individual animals and men vagotomy does little harm and can promptly bring about the cure of an ulcer.

In a few individual animals and men vagotomy produces much discomfort and ill health and, in animals, it can even result in decline and death. Why there is this individual difference is not yet known.

Vagotomy does not always protect animals and men from the production of ulcers. In fact, in some individual animals and men it leads to the production of ulcers.

Since vagotomy must usually be done in addition to gastro-enterostomy or partial gastric resection, what is most needed today is an answer to the question: Will vagotomy prevent the formation of a jejunal ulcer? Already, reports are coming in of cases in which a bad jejunal ulcer developed after vagotomy (Warren (207), Walters (117)).

It is interesting that the flurries of interest in bi-vagotomy in the years 1907 to 1914, 1920 to 1924 and 1930 to 1934 died down. As so often happens, the reasons for surgeons' having given up the operation were not published.

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CARCINOMA OF THE PANCREAS: OPERATIVE PROBLEMS

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Although Halsted had resected the ampulla of vater in 1898 and Mayo had resected the head of the pancreas in 1927, it was not felt that the pancreas was amenable to radical surgery until 1935. In that year Whipple first described the modern operation for removal of the pancreas and duodenum.

Blood, antibiotics, better anesthesia, better understanding of fluid, electrolyte and nutritional balance have widened the scope of all operations. Radical resections for carcinoma have thereby entered a new surgical era. The technic for removal of the pancreas is approaching standardization and the mortality is decreasing; hence an added responsibility for early diagnosis is placed upon us, since these cases are no longer 100% hopeless.

The problem of early diagnosis of cancer of the pancreas has always been difficult. Only $\frac{2}{3}$ of the patients are jaundiced. Though it is usually progressive, there may be remissions. Certain misconceptions regarding the importance of jaundice as a diagnostic sign should be corrected, and upper abdominal pain substituted as the cardinal sign of the early stages of pancreatic malignancy. The pain, present in 75% of cases, is epigastric, may radiate to the middle of the back, is usually worse when lying down and eased by sitting or bending forward, thereby lessening the pressure of the mass upon the posterior abdominal structures. It has no relation to meals or bowel movement and exhibits a steady progression in severity. Sometimes it is paroxysmal, resembling gall stone colic or even peptic ulcer. Unexplained weight loss, with anorexia and gastro-intestinal symptoms, frequently a chronic unexplained fever, are suspicious of cancer of the pancreas. The outstanding early symptoms are profound weight loss and upper abdominal pain.

Physical findings, except for weight loss, may be entirely negative. If one can feel a fixed mass that transmits an aortic impulse, this aids in the diagnosis. However only about $\frac{1}{3}$ of the cases have a palpable tumor (1).

Laboratory findings also give slight help in the diagnosis. Disturbed carbohydrate metabolism is very suggestive of pancreatic disease, but this is rare, as are fatty stools. As the head of the pancreas enlarges, the x-ray may show pressure deformities on the distal greater curvature of the stomach, the cap of the duodenum or the descending or third portion, depending upon the direction toward which the pancreas enlarges.

The diagnostic confusion and uncertainty which plagues us in these cases

before operation, is also only too real at the operating table itself. On the one hand is the fact that a certain number of cases where induration in the pancreas is palpable prove to be chronic pancreatitis, and will get well if left alone and the biliary system drained. On the other hand is the fact that a small carcinoma deeply imbedded in the head of the pancreas (in which case radical removal will give the best chance of cure) does not show itself very positively by any of our present diagnostic methods. One cannot wait until the mass enlarges and causes pressure signs. A small biopsy from the edge of the pancreas will show only chronic interstitial pancreatitis and there will be a certain amount of danger from leakage of pancreatic juice. To get the full benefit of the radical operation it must be done early, often without the benefit of an absolute pathological diagnosis, but after a critical evaluation of all signs and symptoms, none of which are characteristic or diagnostic.

Case 1 illustrates this diagnostic uncertainty at the operating table.

Case 1. Mr. N. B., age 53, first seen Nov. 1, 1944. The patient complained of heart burn for several years, usually following heavy meals and fried foods. About six months ago these symptoms increased so that now even a light meal caused discomfort. This was relieved by soda. There had never been any attacks of sharp abdominal pain. For the past two months he had been on a medical regime which had partially relieved his symptoms. Six weeks previous to admission the patient had noticed that his bowel movements were becoming grayish and light colored but in the last five days they were again becoming normal. Two weeks ago his skin became yellow but this had not increased. He had had 20 lbs. weight loss in the past three months.

Physical examination showed a healthy appearing middle aged man with evidence of weight loss. General examination was essentially negative except for minimal jaundice and a liver palpable 4–5 finger breadths below the costal margin. A questionable rounded mass below the liver was felt by some examiners but not by others.

Icteric index 35. Vandenberg direct 4.77. Indirect 5.35. X-ray: non filling gall-bladder and negative G. I. Series.

Operation Nov. 7, 1944. The liver presented as a shrunken dark slate colored organ not enlarged. There were no irregular liver nodules as had been suspected, but the mass which had been felt was an enormously distended gall bladder. The pancreas was firm and moderately enlarged throughout; its surface appeared irregular and chronically inflamed rather than involved by a malignant process. The gall bladder was aspirated; no stones were found. The common duct was about 1 cm. in diameter. It was opened and dilators passed apparently into the duodenum. There was no marked obstruction at the ampulla. The common duct was drained with a T-tube, pancreas biopsied, and a small drain put in the fundus of the gall-bladder where it had been aspirated.

The biopsy report showed "slight interstitial chronic pancreatitis; no malignancy." Post-operative course was satisfactory. However, the stool did not become normal

deep brown in color, but remained light brown and the external biliary drainage continued. Repeated cholangiograms showed only a small amount of opaque material entering the duodenum.

In May 1945 after some weight gain the cholangiogram still showed only a trickle of lipiodal going thru into the duodenum, and there was dilatation of the hepatic radicals. Several consultations and opinions were sought. The consensus was that it was a slowly resolving chronic intersititial pancreatitis, but because of the duration of the biliary obstruction, it was decided to reexplore. This was done May 17, 1945. A probe in the common duct would not pass into the duodenum so the duodenum was mobilized and then opened. The ampullary opening was found by retrograde probing as a small pin head slit in the mucous membrane, and then was dilated easily to number seven Bakes dilator. It was felt that this should remedy the mild obstruction which was evident at the mouth of the common duct. There was no induration about this area, the pancreas did not seem enlarged and no other pathological change could be seen. The opening in the duodenum was closed, T-tube put in common duct and the abdomen closed.

Post operative convalescence was satisfactory and cholangiogram showed the opaque media entering the duodenum at a much more rapid rate than previously. The T-tube was removed two weeks post operatively and the wound healed quickly. The patient was followed for 4 months and appeared well. Stools were brown in color.

He felt well for over one year. Then he began to complain of epigastric distress, heartburn, belching, and loss of weight.

September 12, 1946, the patient was operated upon elsewhere. At this time a mass could be felt below the liver. The anterior surface of the duodenum was indurated. A biopsy from this area on the duodenum showed "grade 3 adenocarcinoma probably pancreas." A cholecystduodenostomy and posterior gastroenterostomy were done. Convalescence was again satisfactory.

The patient again felt fairly well, but he slowly lost weight, had persistent pain with intermittent jaundice, and a large abdominal mass steadily increased in size. He expired May 27, 1947.

In summary: this is a case of carcinoma of the pancreas which was not evident on two explorations and with several consultants screening all the available data. Two years after onset, and at the third operation the diagnosis was finally made by biopsy from the surface of the duodenum.

The clinical course progressed very slowly. The elapsed time from onset of symptoms to exitus was two and one half years.

Now that resection can be offered the patient, the literature contains many similar cases: i.e. where a second, or third operation disclosed the true state of affairs to be a relatively slowly growing carcinoma of the pancreas which had not been suspected at the earlier explorations.

Some of these, culled from recent reports are: (a) Gall bladder removed 8 months previously, followed by a biliary fistula which closed, then there ensued jaundice and elevated blood amylase. A (pancreatic) tumor was removed in one stage at

the second operation (2). (b) Cholecystostomy for abdominal pain and chills followed by persistent pancreatic fistula for 7 months. At a second operation a (pancreatic) tumor was removed (2). (c) Drainage of an upper abdominal abscess followed by chills and fever. At the second operation a stricture of the common duct was found. At the third operation, 4 months later, a (pancreatic) tumor was found and excised, the patient surviving (3).

Another case, which shows the uncertainty of diagnosis at the time of operation is the following.

Case J. Z., age 62, first seen September 1946. Patient had had chills and fever for two weeks. Jaundice was present at the start, but it disappeared and then recurred again ten days ago and has continued. He had severe localized pain in the right lower chest. He had had a prostatectomy two years ago, and had had an old encephalitis twenty five years previous, which left him with a residual weakness of the right facial nerve, also distinct Parkinson-like mask face and stiff tremor of the fingers. He had lost twenty pounds in the past year.

Examination showed a rather slowly responding man, otherwise in fairly good health. Liver edge was palpable two finger breadths below the costal margin. Icterus was 18. His other tests were relatively normal except for a white blood count of 12,000.

At operation Sept. 14, 1946, the gall bladder was rather markedly distended. There were no stones. The common duct was enormously dilated, fully one and one half fingers in diameter. It was opened but contained no stones and a probe passed easily into the duodenum. The lateral border of the duodenum was free, the pancreas was soft, smooth, and was perfectly normal. "The region of the ampulla contained a small tumor which was easily palpable. It was a softish mass one and one half cm. in diameter and was exactly in the region where the probe went into the duodenum." It was decided that it was not advisable to do any further procedure at this time. The common duct was drained with the idea of exploring this tumor, if necessary, later.

Although the patient had been very well prepared pre-operatively, the post operative inanition, ileus and biliary drainage threw him off his nutritional balance, and on the fifth day he eviscerated his entire wound. This was immediately sutured. Convalescense from then on was smooth, although the protein level was slow in regaining its normal value. A cholangiogram taken Sept. 28, 1946 (fourteen days after the operation) showed the opaque substance passing quite readily into the duodenum. The common duct was clear. Because of this it was decided to do nothing further. In due course the common duct tube was removed. He has been well since and has had no complaints. When last seen Sept. 15, 1947, he had gained seventeen pounds in the last two months. His color was clear and he had had no further pain.

Granting, of course, that this patient continues to stay well one might speculate as to the cause of his obstruction. Evidently, it could not have been a tumor, otherwise he would not have responded as well as he did post-operatively. There

were no stones visualized at the time of the operation. It is conceivable that a small stone was impacted in the ampulla of vater and this gave the sensation of a tumor mass at the time of the operation, when the papilla was palpated between the two fingers of the operator's hand. However, no other manipulations were done to cause the stone to pass. Catell (4) mentioned this same difficulty. Carcinoma of the ampulla is more slowly growing than cancer of the pancreas and most of them are suitable for resection. A tumor of the ampulla 1–2 cm. in diameter may be found 3–6 months after it had produced obstruction to the common bile duct. "We have explored 3 cases at a second stage, in which a tumor was palpated at the first stage, without finding a tumor, and one resection was carried out in a fourth patient with a palpable tumor but cancer could not be demonstrated microscopically" (4).

Case 3. Mrs. R. W., age 55, white female, was first seen June 28, 1946, in the hospital. She complained of acute abdominal pain in the epigastrium and upper right quadrant, going thru to the back. The pain had been present for 5 days. Examination revealed abdominal tenderness in the upper right quadrant and the epigastric regions but no masses and no spasm. Laboratory examinations: R.B.C. 3.49: 10.5 gram, W.B.C. 5,200: 52% polys.: 2% Eosin. 12% Mon. 32% Lymph. Urine negative. X-ray flat plate negative. After twenty four hours rest the patient's pain subsided and she insisted upon leaving the hospital and would not complete her x-ray examination. It was felt that she had had an attack of acute cholecystitis but the anemia could not be explained.

The patient was next seen four months later. She had had no pain since she had left the hospital. Her appetite was good. There was no change in bowel habits, but she had lost 5–6 lbs. and had noticed increasing weakness.

For the past 4–5 days there had been epigastric pain of low grade severity. Jaundice developed 2–3 days ago and stools were now clay colored, urine dark.

Physical examination was essentially negative except for tenderness in the right upper quadrant. R.B.C. 3.72, 11 grams, W.B.C. 7,850, Serum chloride 613, Serum amylase 200, Icterus Index was 85, 3 days later it was 104, and in another 6 days it was 110.

X-ray of gall bladder area was negative for stones. Ingested Barium passed thru the stomach and duodenum but there was evidence of extrinsic pressure on the lateral aspect of the descending portion of the duodenum, displacing and compressing it toward the midline.

At laparotomy (Nov. 4, 1946) the gall bladder was distended and blue in color. The common duct was dilated to 2 cm. diameter but there were no stones. A very hard mass could be felt in the head of the pancreas. Biopsy with frozen section revealed a rapidly growing adeno-carcinoma.

Because of the intense jaundice, pancreatic resection was not attempted and a rapid cholecystjejunostomy was done as the first stage. The jaundice soon subsided and the patient went home. One month later the patient reentered the hospital. For about a week she had been vomiting about 1 hour after eating and she noticed that it consisted of food just eaten; no blood or coffee ground material.

X-rays now showed the descending portion of the duodenum to be partially ob-

structed by an extrinsic tumor. The deformity had greatly increased since the films taken one month previously.

After adequate preparation (gastric suction for 4 days and high protein, high caloric, high vitamin diet, transfusions, etc.), a resection of the pancreas and duodenum was contemplated. However, when trying to dissect around the middle colic artery and vein it was soon evident that they were engulfed by the pancreatic tumor. Resection was not considered advisable: therefore an anterior gastro-enterostomy was done to relieve the duodenal obstruction. The patient made a normal recovery from this operation and was discharged eating well.

The patient got along well for 4 or 5 months, but then began having abdominal pain, indigestion on eating solid foods, weakness and weight loss. June 1947, jaundice and abdominal masses were evident, and exitus followed in July 1947. Thus the elapsed time from first symptom to exitus was one year; palliation was about 4 or 5 months.

Two operations and three hospital admissions gave this patient palliation only. Her case presented several problems which, in retrospect, are instructive. (1) Following an initial gall-bladder-like colic, she remained well 4 months, then had sudden obstructing jaundice and from that time on there was rapid progression. There are three types of pain associated with carcinoma of the pancreas. (a) steady dull severe mid epigastric pain radiating to the lower back. (b) paroxysms of severe umbilical pain radiating upward to the back and front of the chest and (c) colicky pain in the right hypochondrium simulating gall stone colic (1). This patient had had the third variety, and there was only one warning. To apprehend such cases early enough for radical surgery to be curative, every such attack in a middle aged person must be viewed with suspicion and alarm. Certainly that is not our usual practice today. (2) Whipple's first description of the operation was a two stage procedure. The one stage procedure is now preferred if the patient is in suitable condition. Since the discovery of Vitamin K the jaundiced cases may be done in one stage as the bleeding tendency can be controlled. This does away with troublesome adhesions, reduces the possibility of metastasis and shortens the hospital stay. Crile (5) has recently reported a one stage resection in a jaundiced man, aged 78. Whipple (6) advocates one stage, reporting twenty-one one stage and eight two stage procedures. However, Catell (4) and others feel that markedly jaundiced patients must still be done in two stages. By and large, these are the ones who come to operation most frequently (4). This was our judgment at the time, but even though the delay was only one month, at the second exploration the lesion was rapidly growing and involved the middle colic vessels.

(3) How radical can one be in the removal of such a lesion? Certainly sufficient tissue must be removed to include any local infiltration. With most

authorities, any regional lymph node involvement is a contraindication to radical resection. Brunschwig (7) however defines inoperability as involvement of the termination of the superior mesenteric vein and of the first segment of the portal vein. For him, involvement of the middle colic vessels necessitating removal of the transverse colon, is no contraindication. Recently Schaffer (8) has devised a superior mesenteric-vena-caval shunt, so that the head of the pancreas together with the patent portal vein may be resected and the venous drainage of the viscera re-established between the superior mesenteric vein and the vena cava.

(4) Another limitation which is not easily measured is the type of growth and rapidity of spread. By and large, the successful cases are the slowly growing ones. In the above case the elapsed time from first symptom to inoperability was 6 months. In the reports so far available, such rapidly growing cancers are not cured.[1] To have gone through such a surgical ordeal, comprising 4–5 hour operations, perhaps several weeks of stormy convalesence then to have recurrence take place in 2-3 months, and the total illness to be less than 1 year may constitute a surgical miracle to the laymen, but the actual accomplishment, in retrospect is not great, and that is the final sentiment of the patient's family.

However, there are slowly growing carcinomas of the pancreas even though the usual figures given in medical texts are 6 months to 1 year from the first symptom to death. One case in our experience lived 4 years after exploration and proven biopsy (9). Carcinoma of the ampulla, numerically a small group, constitute a larger percentage of cases which have done well after operation. Catell's (4) series of 18 resections contained 13 ampullary growths. They grow and metastasize more slowly than the average pancreatic cancer.

These radical methods for resection of the pancreas have extended the field for resections of gastric carcinoma. The technical problems are the same. Growths which have infiltrated into the pancreas, and hitherto have been inoperable, now must be re-evaluated as regards operability.

The following case illustrates this.

Case 4. Mr. M. R., a 69 year old male first seen on Jan. 2, 1947 complaining of progressive constipation, ease of fatigue, and 30 lb. weight loss over a period of six months. He had had increasing weakness, anorexia, flatulence after meals for 2 months. There had been no vomiting or abdominal pain. X-rays 1 week ago had

[1] (a) Painless jaundice 3 weeks without other clinical manifestations. Radical resection. Survival 5 months (Varco, 10).
(b) Progressively increasing jaundice 2 months. Patient survived operation 3 months (Mullen, 3).
(c) Increasing jaundice 3 weeks. Conservative treatment for 6 weeks. Then 2 stage operation 3 weeks apart. Patient survived 4 months (11).
(a, b, c) Quoted by Elman and Schwartz (12).

shown nearly complete pyloric constriction with a greatly dilated stomach. He had been unable to eat since then.

Physical examination revealed an acutely and chronically ill man lying quietly in bed. The abdomen was moderately distended. There was no tenderness, muscle spasm or palpable masses.

Admission laboratory work: Free HCL—none, total 102. Serum chloride, 467 mgms. NPN, 26. Serum protein, 4.46 gram. R.B.C 3.15, HB 8.0 gram, WBC 8,400, Urine negative, FBS 120.

With intubation and gastric lavage with dilute HCL for 4 days the pyloric obstruction was relieved, and the patient was able to take a high caloric, high protein fluid diet (2500 cc, 2500 cal.). This plus repeated blood transfusions brought the serum chlorides to 526 and total proteins to 6.68 with A/G ratio of 1.8/1.

On Jan. 11, 1947 an abdominal exploration was done under intratracheal ether anesthesia. A large carcinoma of the stomach was found, involving the lesser curvature and posterior wall, densely adherent to the mid portion of the pancreas, and extending over onto the duodenum beyond the pylorus. The greater omentum was dissected up, and the pylorus-duodenum region exposed. The growth involved the duodenum for fully one inch beyond the pyloric sphincter, and when the common duct was freed, it was seen to be close to the edge of the growth. Resection would require transplantation of the common duct. In spite of the local extent and spread of the growth, there were no gross metastases in the liver or the neighboring glands, and since the patient was taking the operation well, it was decided to proceed.

The common duct was divided at its duodenal entrance, the pancreatic duct was identified emptying into it ½ cm. proximalward, and the duodenum transected in its 3rd portion just proximal to Treitz ligament. The head of the pancreas seemed normal, but the midportion was involved in the growth. A segment of pancreas 2″ in width was removed just distal and to the left of the middle colic vessels. The tail, and the remaining portion of the head were sutured together by heavy mattress sutures. The end of the common bile duct was small. It was implanted into the duodenum with a double suture layer, the inner row suturing mucosa to mucosa. This was difficult, and subsequent events showed that anastomosis over a tube would have been better. 2500 cc. of blood was given in the operating room, the blood pressure never dropping below normal.

The immediate post operative condition was excellent. However, bile stained discharge was evident 24 hours later. This increased in volume as the days went on, and soon there was slow separation of the wound, digestion of the tissues in the depth, and in spite of all manner of supportive treatment, exitus occurred suddenly on the 17th post operative day. The serum proteins could not be raised above a low level, but otherwise the chemical balance was maintained.

Autopsy showed marked pancreatic necrosis with complete digestion of the anterior portion of the gastro enterostomy suture line, and plastic adhesive peritonitis. There was no further gross extention of the carcinoma.

In retrospect: although authorities favor mucosa to mucosa suture of such things as common duct implantations, if the parts are too small, anastomosis over vitallium

or rubber tube is preferable. Also, the tail of the pancreas might have been removed, since the remaining distal end sloughed.

Whipple, in his original communication, divided and closed the distal end of the stomach, ablated the duodenum and pancreas, closed over the tail of the pancreas, made a posterior gastroenterostomy and anastomosed the gall bladder fundus to the stomach.

The operation has undergone an evolution and standarization since then. Hunt in 1941 implanted the pancreas into the small intestine while Cole, Whipple, and Trimble independently in the same year reported a one stage operation consisting of antecolic anastomosis of the cut end of the stomach and also of the common duct into the jejunum.

With minor deviations, the following fundamentals have been agreed upon:

(1) Determine whether the tumor can be dissected from the superior mesenteric vessels and portal veins early in the operation. The peritoneum along the lateral curvature of the duodenum is incised and the duodenum with the head of the pancreas is lifted up, the portal vein is explored and separated away. The dissection is begun inferiorly and laterally, ligating the pancreatic-duodenal arteries after the operability of the tumor has been definitely established and not before.

(2) Implantation of the common duct into the jejunum is accomplished either with end of duct to side of jejunum, or end of duct to end of vertical limb of transected jejunum. If done in two stages, the first stage consists of anastomosing the gall bladder fundus to the jejunum, preferably, and ligating the common duct carefully at the second stage.

(3) Anastomosis of the pancreas end into the jejunum below the bile duct anastomosis. This prevents external pancreatic fistula and restores the pancreatic secretion to the intestinal tract. This may be done by using a small № 12 catheter in the main duct or by free implantation using mucosa to mucosa sutures.

(4) Make the gastro-jejunostomy opening the most distal of the three anastomoses, so that the food stream will not pass over the transplanted end of the common duct, causing ascending cholangitis.

(5) As regards anterior or posterior gastro jejunostomy, there is no difference, the choice being determined by the length of the jejunal mesentery and the thickness of the transverse meso colon.

Thus, the mechanical limitations of resections are being continually extended as technical improvements develop.

Figures collected to date show that many large clinics have 30 to 40 cases in their series. The mortality is now about 20 to 30% but was about 35% 2 years ago. It is interesting to note in one series 22.2% mortality for radical and 43.3% for palliative procedures.

Whipple has reported one resection for carcinoma of the pancreas alive five years after operation (13). Two cases have been reported who have lived 33 months. About one out of nine cases has been reported to live 24 months, but many cases are reported to be alive and well up to one year. Since over half of the resections done to date were done in the last two years, it is too early to state positive conclusions regarding prognosis.

SUMMARY

Four cases are discussed illustrating certain problems in the operative handling of carcinoma involving the pancreas. The development, indications and limitations of the modern radical operation are discussed.

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AMEBIASIS IN VETERANS OF WORLD WAR II WITH SPECIAL EMPHASIS ON EXTRA-INTESTINAL COMPLICATIONS, INCLUDING A CASE OF AMEBIC CEREBELLAR ABSCESS

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A number of observers have predicted an increased incidence of amebiasis at the termination of the war (3, 11, 29, 35). These predictions were made on the basis of the known exposure of American troops to unsanitary environments where the native population was highly infected. This eventuality was envisioned in spite of the fact that competent observers have pointed out that from .10 to 20% of the American population shows the presence of *E. histolytica* in the stools (1, 4, 5, 6, 8, 18, 23, 25, 35). Not all surveys, however, were that pessimistic, as exemplified by one survey from Maryland which claims only 0.2% incidence of this parasite (1). One, of course, must keep in mind in such surveys the diligence and experience of the examiners as well as the number of stools examined.

This report is of special significance since Chicago, following the 1933 experience with amebiasis, has been regarded as a highly endemic zone above the Mason-Dixon Line. This study is not based on a survey of hospital patients in whom stools were examined routinely. All these patients entered Hines Veterans Administration Hospital because of symptoms referable to the gastrointestinal tract or due to complications of amebic infection. From January to August 1946, 12,000 patients were admitted to this Veterans Hospital; of these 58 were diagnosed as suffering from amebic colitis or its complications. In the last calendar year before the war, of 9,000 admissions to this hospital, only 8 were diagnosed as amebic colitis. That is, the post-war incidence of this disease is 5 times greater than before. In 1933, when a general rise in the incidence of this infection was reported for the Chicago area (31), only 2 cases of intestinal amebiasis and one amebic abscess of the liver were recorded among 5,000 admissions. Furthermore, all our cases were seen among veterans of World War II, although the general admission to this hospital shows a considerable number of World War I veterans. Also, as will be pointed out later, most of the victims of this infection served in tropical or sub-tropical zones. All of these factors confirm the suspicion that the returned veterans will magnify the incidence of this infection among our population.

Another significant factor in our group of cases is the high incidence of hepa-

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tic complications. Of the 58 cases, 8 had an amebic abscess of the liver, and 7 had amebic hepatitis, or an incidence of 27%. One of the cases of liver abscess developed a brain abscess. This incidence of hepatic complications is much higher than that reported by other observers (14, 17, 21, 22, 24, 27, 28). The incidence of hepatic abscess in patients infected with *E. histolytica* is usually given as about 5 per cent (3, 21). The incidence of hepatic complications in our group is indicative of virulence of the strain of the organism.

AMEBIC COLITIS

The cases with amebic colitis do not require extensive comment. They were all symptomatic, and therefore, had clinical evidence of activity. Thirty-three of the 43 patients with intestinal amebiasis came in with diarrhea. A few of the others had a previous history of diarrhea, and the others abdominal pain and/or tenderness pointing to the gastro-intestinal tract as the seat of the trouble. We do not intend to imply from this that the majority of the patients complaining of the above symptoms would show *E. histolytica* in the stools. While we have no available statistics on this point, we feel quite sure that our experience would prove to be in agreement with a recent report that only 10% of soldiers complaining of diarrhea showed pathogenic organisms in the stools (12).

Among the patients with amebic colitis who presented themselves with diarrhea, the motile form of the organism was frequently found and the sigmoidoscopic examination revealed the presence of ulcers (table 1). Thus, of the 33 patients with this symptom, 34 revealed the presence of trophozoites in the stools; of these, 8 also had cysts in the stools. Nine, however, were found to have cysts only. Twenty-seven of these patients had sigmoidoscopic examinations, 19 of which were found to have amebic ulcerations within the reach of the sigmoidoscope. This is in contrast with 11 patients who did not have diarrhea as a presenting symptom and none of whom had trophozoites in the stools. Only 3 of these were sigmoidoscoped and all with negative results. One would expect, therefore, to find positive sigmoidoscopic evidence of disease in cases with diarrhea, if the etiology of this is the *E. histolytica*.

Several helminths were found in the stools along with the *E. histolytica*. Two had hookworm ova, one *Giardia lamblia*, two *Trichiuris trichiura*, and one *Ascaris lumbricoides*. Other complicating diseases were malaria in 5 and infectious hepatitis in 1. The latter case presented a problem in differential diagnosis. It was nevertheless of interest to determine whether any correlation existed between areas of service and the incidence of the disease. At least one recent report purports to discount the probability that soldiers who have served in certain areas of the world were more likely to become infected with *E. histolytica* (17).

Of the 7 cases with amebic hepatitis, 4 served in the Pacific Theatre and 3 in the China-Burma-India Theatre (Chart 1). In the cases with frank abscess, 5 served in the Pacific Theatre, and 1 each in the Mediterranean, European, and American Theatres. Only 1 of these did not serve overseas, and he was stationed in the southern part of the United States. Only one veteran each served in the European and Mediterranean Theatres, whereas, more troops

TABLE I

Amebic colitis, laboratory and proctoscopic findings

	DIARRHEA	NO DIARRHEA
Number of cases	33	11
Trophozoites	16	0
Cysts	9	11
Trophozoites and cysts	8	0
Proctoscopic examinations	27	3
Amebic ulcers	19	0

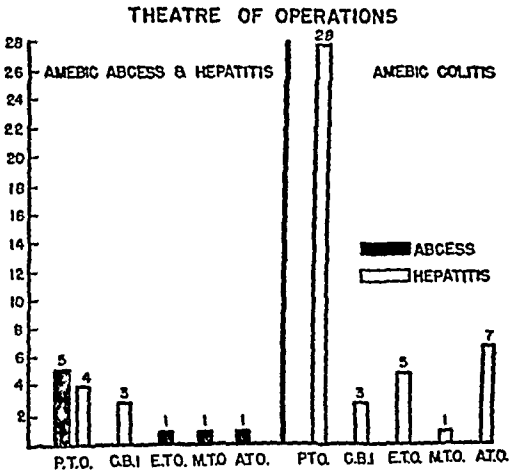


CHART 1. SHOWING THE DISTRIBUTION OF PATIENTS ACCORDING TO THEATRE OF OPERATION

were engaged in these Theatres than in the Pacific. This increases the importance of the difference.

In examining the cases with amebic colitis, the same situation is revealed. Twenty-eight of these veterans served in the Pacific Theatre and 3 in the China-Burma-India Theatre, or 31 of 44 or nearly 75% of the entire group. Only 5 served in the European Theatre and 1 in the Mediterranean Theatre. Seven of this group saw no service overseas. Thus, among the group of intestinal amebiasis an imposing majority (75%) served in highly endemic tropical areas. This seems to be more than coincidence.

AMEBIC ABSCESS AND HEPATITIS

Clinical picture. The clinical picture of the hepatic complications of amebiasis is such as to be easily confused with other conditions. Hence, the diagnosis is frequently missed for a long period of time, specific therapy withheld, and the patient's life and chances for recovery are jeopardized. One reason may be, as pointed out by Sodeman (31) and Walters (34), that this condition is not thought of frequently enough, especially in non-tropical regions. The patient's presenting complaints and physical findings may focus the physician's attention elsewhere, e.g., the respiratory system.

The case histories of several representative cases will be outlined and then followed by a discussion of the symptoms, signs, and laboratory findings in the whole group.

CASE HISTORIES

Case 1. D. K., white male, age 36 was admitted to the hospital October 22, 1945, with the complaints of generalized abdominal cramping pains and the passage of bright red blood in the stools followed by a diarrhea of 4 to 5 stools daily. Although he served in the Pacific Theatre, he denied any previous diarrhea. The physical examination at the time of admission was essentially negative. The patient was afebrile and except for a mild anemia, did not look particularly ill.

Laboratory examinations revealed an R.B.C. of 3,720,000, W.B.C. of 5,850 with a normal differential count. Smears for malaria were negative and agglutination tests for typhoid, paratyphoid, and brucella were negative. The stools contained occult blood for several days but later this disappeared. On one occasion, a small motile ameba was found, but this was not thought to be an *E. histolytica* organism.

The suspicion was that he had bled from the colon, but a sigmoidoscopic examination was negative as was a barium enema x-ray of the colon. The stomach and duodenum were negative for peptic ulcer or any other organic pathology.

His diarrhea quickly subsided without any specific therapy.

On November 24, the patient's temperature rose, and he continued running a febrile course, with temperature peak in the afternoon reaching nearly 104°F., but in the morning the temperature was usually normal.

Concomittantly he began complaining of pain in the region of the right scapula and right lower chest, which pain was related to deep inspiration. Definite tenderness was elicited in the right upper quadrant and over the lower intercostal spaces in the axillary line. The W.B.C. rose to 18,000 with 63% polys, 36% lymphocytes, and 1% eosinophiles. Numerous smears were done for malaria and all were negative.

Beginning on December 6, the patient was given 1 grain of emetine HCl daily for 6 days, and the fever decreased to normal within 4 days, but began rising again 2 days after the emetine was discontinued, again reaching a peak of 104. On December 29, the right lobe of the liver was aspirated through the 8th intercostal space in the anterior axillary line and 180 cc. of chocolate colored "pus" was removed. The

temperature promptly dropped to normal and remained normal until the 6th of January, 1946, when it again began to rise and emetine was again administered and continued for 7 days. On the 12th of January, another 80 cc. of "pus" was removed by aspiration, and the patient then made an uneventful convalescence.

No amebae were demonstrated in the aspirated material.

Case 2. W. E. G., white male, age 24 was admitted to another Veterans Hospital February 20, 1946, because of chills, and fever, and pain in the epigastrium and under the right costal margin, of several weeks duration. He was transferred to Hines Veterans Administration Hospital on March 11, 1946, with essentially the same symptoms.

His past history consisted of a bout of diarrhea, blood streaked, in May, 1945, while serving in the South Pacific. This diarrhea persisted for 5 weeks. He was well until his return to the United States, in December, 1945, when he began having chills and fever which appeared to respond to atabrine. However, several weeks later, he lost his appetite, fever returned, and upper abdominal pains began. He also had a recurrence of the diarrhea. The pain was dull and aching in character and continuous. Ingestion of food would bring on cramping upper abdominal pain. His urine became dark.

Physical examination revealed an acutely ill white male who was obviously in a good deal of distress. There was a moderate icterus of the sclerae and skin. The right leaf of the diaphragm was found to be elevated about 4 cm. as compared to the opposite side. This elevation was more noticeable posteriorly and in the right axilla. There was a suppression of breath sounds in the right base.

The abdomen was found to be distended, and there was a visible prominence of the right upper quadrant of the abdomen. The liver extended down to the umbilicus, was smooth and markedly tender. A point of exquisite tenderness was found in the 9th interspace close to the right anterior axillary line.

The clinical impression was of amebic abscess of the liver.

The blood showed a mild anemia, R.B.C. of 3,5000,000 and hemoglobin of 10 Gm. The W.B.C. revealed a leucocytosis of varying degree. One W.B.C. was reported as 24,200 and another as 21,000; the others varied between 13,700 to 18,200. The polymorphonuclear leucocytes were on one occasion 80%, but at other times, were about 75%. Three per cent eosinophiles were reported on several occasions.

Stools examined on numerous occasions failed to reveal *E. histolytica* cysts or trophozoites.

The blood showed an icteric index of 26, the urine showed some bile, and urobilinogen. The quantitative urobilinogen was 1.6 mg. per 100 cc. on one occasion. The Takata-Ara reaction was negative, and the cephalin-cholesterol flocculation two plus. The plasma cholesterol was 223, and the esters were decreased to below 50%. The albumin globulin ratio was 1.0. A B.S.P. test, using 5 mg. per kilo, showed no retention at the end of one hour. X-ray of the chest revealed elevation of the right diaphragm, and flat plate of the abdomen showed the lower border of the liver at the crest of the ileum (fig. 1).

On March 13, 1946, the patient was put on one grain of emetine HCl subcutaneously daily for 10 doses. After 5 doses, the temperature began to fall, and on the 8th day, reached a nearly normal level (graph 1). In spite of this, the patient still continued to look very ill and complain of pain and exquisite tenderness over the liver. At this time aspiration of the liver was undertaken. Using novocaine infiltration, a needle was inserted in the 9th interspace in the anterior axillary line, and

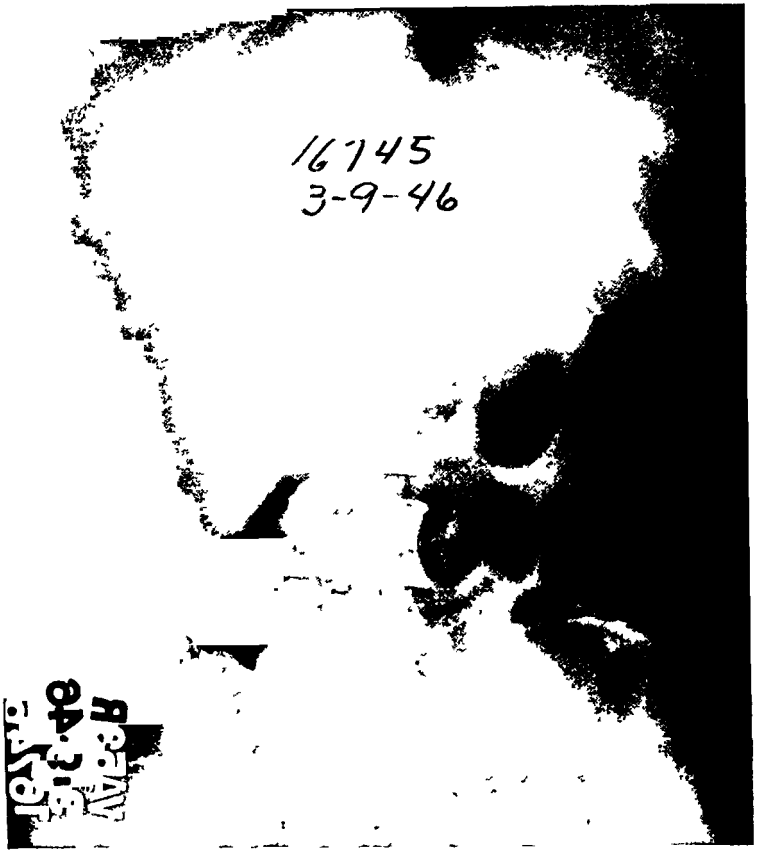


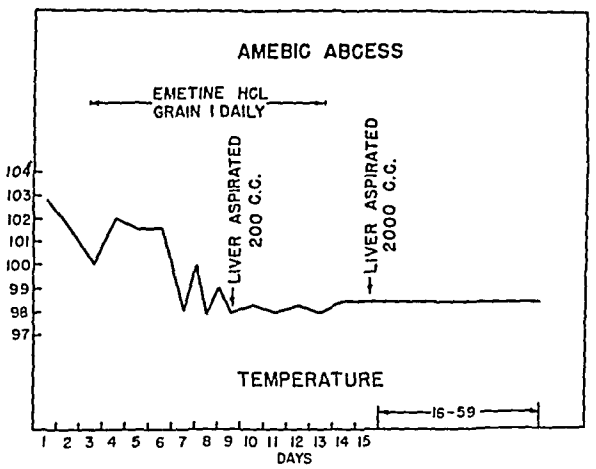
FIG 1 FLAT PLATE OF ABDOMEN OF CASE 2 (W E G) SHOWING ENLARGEMENT OF LIVER DOWNWARD TO ILIAC CREST

although the needle was 1½ inches long and 20 gauge, 200 cc. of a chocolate colored material was removed. Because of the small calibre of the needle, a 16 gauge needle was then inserted in the 8th interspace in the anterior axillary line, pointing the needle upwards and posteriorly, and 2000 cc. of a chocolate colored material was removed. The liver edge then rose from the level of the umbilicus to about 2 fingers below the right costal margin.

In addition to the above therapy, he also received a course of diodoquin orally for

20 days, consisting of three daily doses of 9.6 grains (0.6 gms.) each. The patient continued to improve remarkably, gaining weight and strength. The liver tenderness disappeared completely, and the edge became just palpable at the right costal margin.

Case 3. H. R. S., white male, age 25 was admitted to another Veteran's Hospital on September 22, 1945. He was discharged from the Service on September 3, 1945, in good health. One week following discharge he began to experience a dull dragging pain in the right upper quadrant of the abdomen. About the same time he began having chills and fever. He took atabrine for 1 week without benefit. He was then transferred to Hines Hospital on December 11, 1945, because of the continuation of his fever and chills. A diagnosis of acute hepatitis was entertained as well as hepatoma because the right diaphragm was considerably higher than the left.



GRAPH 1. SHOWING TEMPERATURE OF CASE 2 (W. E. G.) AS IT RESPONDED TO THERAPEUTIC MEASURES

An additional point in the history elicited was a period of bloody diarrhea of 2 weeks duration while on duty in the South Pacific.

The important physical findings were the acutely ill appearance of the patient, with a septic type of temperature, rising to 103°F. daily with a corresponding increase in pulse rate, and elevation of the right diaphragm which did not move perceptibly on respiration. The liver was palpable about 5 cm. below the right costal margin and was quite tender. There was also tenderness in the lower intercostal spaces and in the right anterior axillary region.

On admission to Hines Hospital, the blood showed a leucocytosis of 16,300 with 81% polys and an anemia of 2,200,000 R.B.C. with a hemoglobin value of 40%. The urine was normal. Repeated stool examinations failed to reveal *E. histolytica.* Serum bilirubin was 0.7 mg. %. The cephalin cholesterol flocculation test was 2 plus. Serum protein level was 7.2 Gm. per 100 cc. with 5.1 Gm. of albumin and 2.1 Gm. of globulin. The intravenous hippuric acid synthesis test showed an excretion of 0.45 Gm. in one hour. The prothrombin time was normal.

X-rays of the chest showed a progressive elevation of the right diaphragm and blunting of the right costo-phrenic angle (fig. 2).

On the basis of the above evidence, a diagnosis of amebic abscess of the liver was made, and a course of emetine HCl, 1 grain daily, was begun on January 2, 1946. Within 4 days, the patient became afebrile. In addition to the emetine, chiniofon was administered orally, 1 Gm. three times daily. Aspiration of the liver was at-

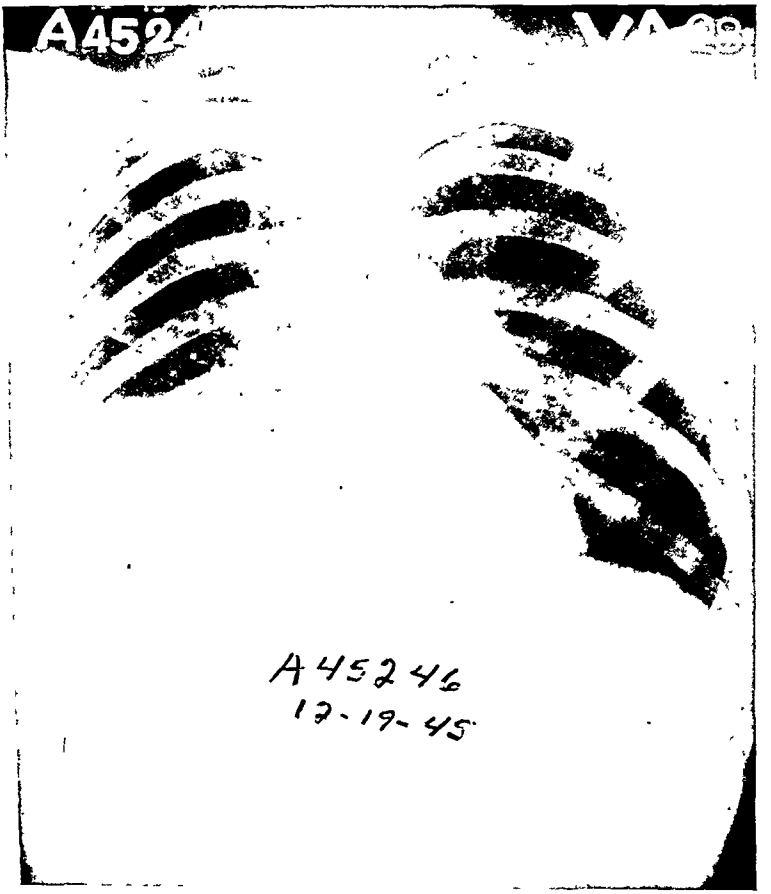


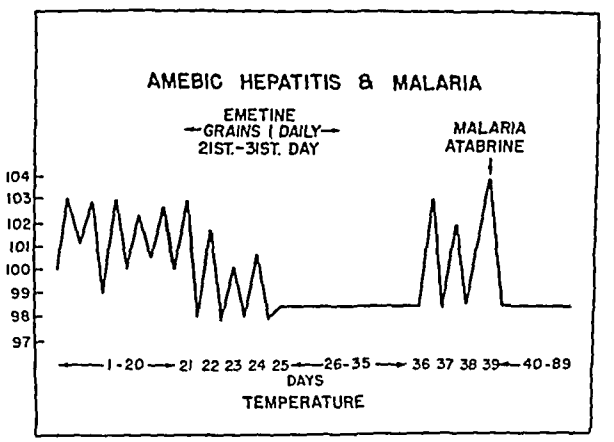
FIG. 2. X-RAY OF CHEST OF CASE (H. R. S.) AMEBIC HEPATITIS BEFORE THERAPY SHOWING MARKED ELEVATION OF THE RIGHT DIAPHRAGM AND BLUNTING OF THE COSTO-PHRENIC ANGLE

tempted, the site being the 9th and 10th intercostal spaces in the anterior axillary, line, but no pus was obtained. Ten days after the discontinuation of the emetine, the temperature rose again (graph 2). His liver at this time had decreased in size, and the tenderness was closer to the mid-line. Another aspiration was attempted, this time going in anteriorly below the costal margin, about 5 cm. lateral to the xiphoid cartilage and again no pus was obtained.

Surgery was considered because of the possibility of a left lobe liver abscess. However, the spleen became palpable, and the white count revealed a leucopenia. A smear of the blood this time revealed *Plasmodium vivax organisms.* Response to atabrine was prompt, and the patient thereafter remained afebrile. The liver and spleen decreased in size and remained non-tender (fig. 3).

This case exemplifies the confusion that may arise when malaria complicates amebic hepatitis.

Case 4. E.L.M., white male, 30 years of age, with 28 months service on Luzon and in New Guinea. This patient was admitted to Hines Hospital on May 18, 1946, complaining of cough, anorexia, fatigability, and loss of 20 pounds in weight since November, 1945. About 5 weeks before admission to the hospital, he noted that the cough was accompanied by pain in the right side of the chest. Fever became apparent at that time also, but it apparently subsided after sulfonamide medication. However, the patient still complained of feeling poorly, having night sweats, until



GRAPH 2. SHOWING TEMPERATURE OF CASE 3 (M. R. S.) AMEBIC HEPATITIS COMPLICATED BY MALARIA, AND THE RESPONSE TO SPECIFIC THERAPY

several days before admission when his chest pain became more severe. Fever recurred, and expectoration of a brownish material commenced.

Physical examination on admission revealed an acutely ill, moderately dehydrated patient. There was a fever up to 104°F. with a corresponding increase in pulse rate. The respirations were 26. The chief findings were referable to the chest and consisted of some decreased excursion of the right side of the chest, and dullness to flatness in the right base and axilla, and the right diaphragm did not seem to move. The breath sounds were suppressed in the right base, and crepitant râles were audible. Although the liver was not palpable, some tenderness was present in the right upper quadrant of the abdomen.

The R.B.C. was 4,000,000, hemoglobin 75%, and the W.B.C. 19,000 with 88% polys and 12% lymphocytes. The urine was negative. The sedimentation rate was normal. X-ray examination of the chest revealed a hemogeneous density in the base of the right lung, which was first interpreted as a pneumonitis with pleural effusion (fig. 4).

The patient was treated with penicillin intramuscularly, and although the fever subsided somewhat, he continued to cough, have chest pain, and expectorate chocolate colored sputum.

The latter was suggestive in appearance of material obtained from an amebic liver abscess, and although the patient did not recollect ever having had diarrhea, *E. histolytica* cysts were found in the stools. At the same time, the roentgenographic

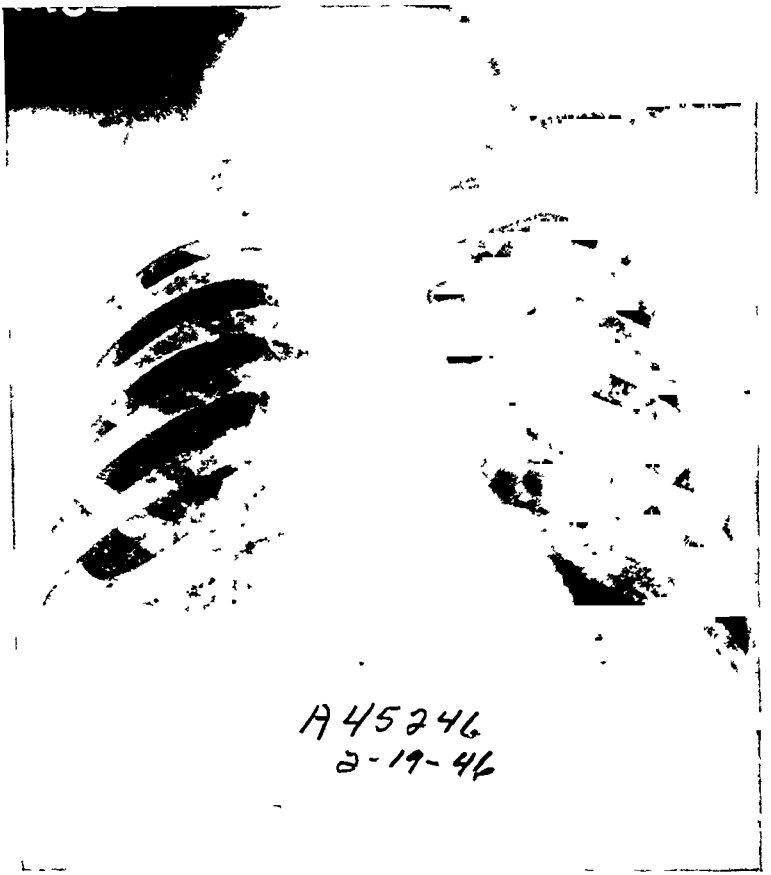


FIG 3 CHEST X-RAY OF CASE 3 (H R. S) SAME AS FIG 3, AFTER THERAPY
Note the disappearance of the elevation of the right diaphragm and the clearing of the right costo phrenic angle

appearance changed (fig. 5). An abscess in the right lower lobe became apparent, the source of which appeared to be a liver abscess.

The patient was placed on emetine HCl, one grain daily, and carbarsone, 0.25 Gm. twice daily. Immediate symptomatic improvement was noted with decrease in the chest pain and expectoration.

The x-ray showed progressive healing of the abscess cavity in the right base with only residual tenting of the right diaphragm (fig. 6).

Case 5. W. G., colored male, age 40 was admitted to Hines Hospital on June 30, 1946, complaining of a "chest cold" of 2 weeks' duration, right upper quadrant pain, and fever. The pain was aggravated by deep breathing and coughing.

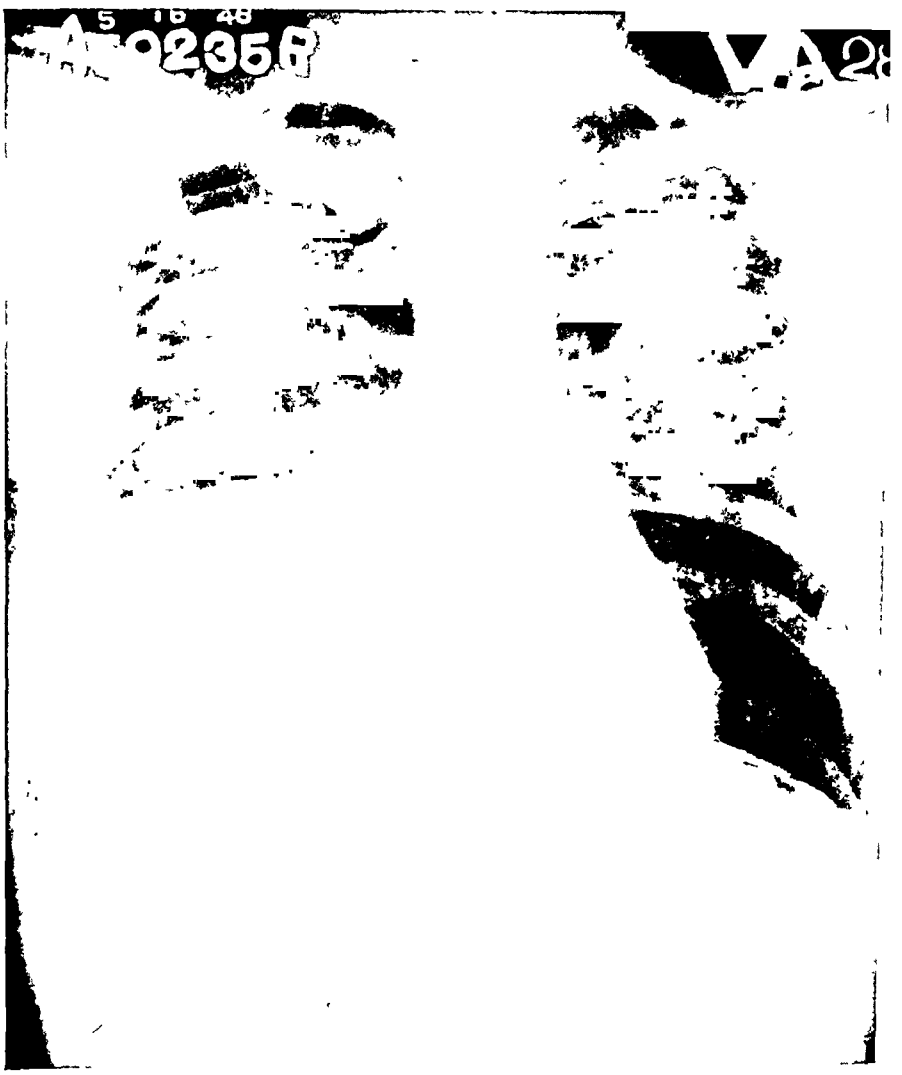


FIG. 4. CHEST X-RAY OF CASE 4 (E. L. M) SHOWING ELEVATION OF RIGHT DIAPHRAGM WITH SOME PARENCHYMAL INVOLVEMENT OF THE RIGHT LOWER LOBE

He served in the Army in the European Theatre, and lived most of his life and was also stationed while receiving his Army training in the southern part of the United States.

The significant point in his past history was the fact that while stationed in England in May of 1944, a liver abscess was drained surgically.

On physical examination, neither the liver nor spleen were palpable, but tenderness was present over the liver area on palpation and percussion. The diaphragm was found elevated on the right side, otherwise the findings in the chest were negative.

The patient continued to run a septic course, and his general condition was poor. *E. histolytica* cysts were found in the stools, and the patient was placed on emetine HCl, ½ grain daily for 12 days, and diodoquin, 9.6 grains three times daily for 20 days. The liver became larger until it extended 3 fingers below the right costal

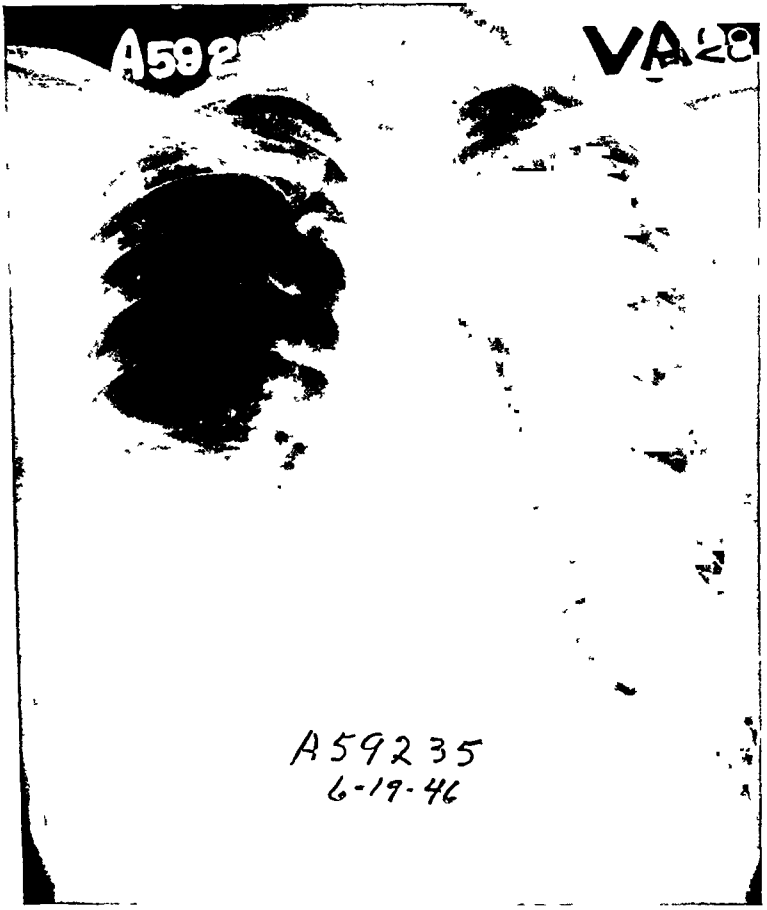


FIG. 5. CHEST X-RAY OF SAME PATIENT (E L M) AS IN FIG. 4 ONE MONTH LATER
Note changes in right base suggestive of lung abscess

margin. The W.B.C count rose to 16,000. The B.S.P. test showed no retention, and the urine urobilinogen remained negative.

On September 18, 1946, the temperature rose to 103°F. and was preceded by a chill. He complained of pain in the right shoulder and periumbilical region. The abdomen became rigid, and no peristaltic sounds were audible. An exploratory laparotomy was performed that same day and a brownish material was found in the peritoneal cavity. This appeared to arise from a perforated hepatic abscess.

Shortly after the surgery, glycosuria was noted, and on September 28, the fasting blood sugar was 294 mgm. %. A repeat blood sugar on October 1 was 357 mgm. %. The patient was placed on insulin, but the hyperglycemia and glycosuria rapidly improved so that insulin was discontinued on October 10, 1946.

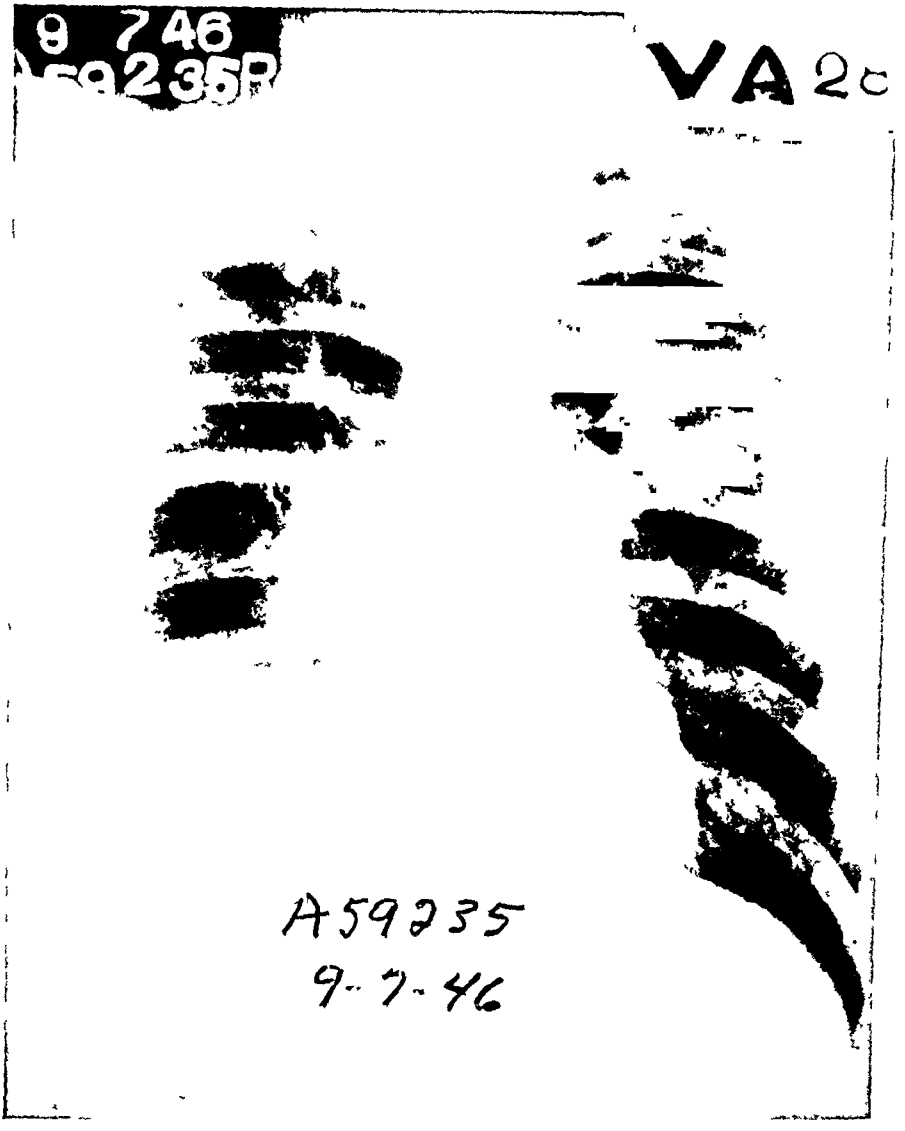


FIG. 6. X-RAY OF CHEST OF SAME PATIENT (E. L. M.) AS IN FIG. 4 AND 5 AFTER SPECIFIC THERAPY
Note clearing of density in right lower lobe

The patient, however, continued to run a septic fever, and the right diaphragm showed further elevation. On October 18, a posterior thoracotomy for drainage of a subphrenic abscess was performed. In spite of profuse drainage from the abscess cavity, he continued to run a fever up to 102°F. daily, and his general condition remained poor.

On November 19, while tying his shoes, he fell out of bed. Two days later nystagmus to the left was noted as well as exaggerated reflexes and weakness of the left side of the face. A spinal tap revealed clear spinal fluid with 5 cells per cubic mm. and a questionable increase of protein. The same day, the patient went into coma and expired.

Autopsy revealed the following outstanding findings: The liver weighed 2,500 gms. The superior surface was adherent to the abdominal surface of the right diaphragm, and the posterior surface of the liver to the posterior abdominal wall. When the diaphragmatic adhesions were separated, a subphrenic abscess was encountered. This abscess measured 8 by 3 cm. and did not communicate with the surgical opening in the posterior chest wall. The surgical wound did, however, communicate with a posterior liver abscess measuring about 10 cm. in diameter. On section of the liver, a third abscess was found which did not communicate with the other two. The contents of these abscesses was a pinkish-gray, thick liquid.

The other important gross finding at autopsy was in the cerebellum. The left cerebellar hemisphere was the site of an abscess cavity, 2.5 cm. in diameter. The abscess cavity communicated with the left lateral sinus which also contained purulent material.

The gastro-intestinal tract showed no ulceration.

Microscopically the wall of the liver abscess was seen to be composed of granulation tissue. The liver parenchyma adjacent to it was completely destroyed and replaced by fibrous tissue. Infiltration of plasma cells and lymphocytes was present. Due to compression, there appeared to be an increase of the bile radicals. An occasional mononucleated ameba was seen.

The wall of the cerebellar abscess was seen to be composed of necrotic brain tissue. Many lymphocytes and occasional polymorphonuclear leucocytes and mononuclear cells were seen. This abscess appeared to be more recent and acute than the liver abscess.

DISCUSSION OF COMPLICATIONS

To the clinician, one of the most important phases of hepatic complications of amebiasis is its diagnostic pitfalls. Delay in diagnosis should be avoided since early treatment is satisfactory, whereas, delay in treatment may spell disaster. The diagnostic difficulties depend on two factors: the clinician's lack of awareness of the condition, and secondly, its confusing symptomatology. Since the incidence of this complication, even in temperate zones, is rising, amebic hepatitis and abscess should be kept in mind as a diagnostic possibility in a variety of clinical pictures.

The conditions that this complication may be confused with are many, and include diseases of the chest, such as pneumonia, and pleurisy, and other hepatic diseases, such as cirrhosis and hepatitis as well as cholecystitis and cholangitis. Diseases of other abdominal organs may be mimicked. Subphrenic abscess from perforation of a hollow viscus is a frequent confusing issue. Abdominal

Hodgkin's disease, as well as systemic infections such as malaria, is also a differential diagnostic possibility which may be a complication as was the case in one of our patients. The varied symptoms and findings account for this confusion.

The commonest symptom in our 15 cases of amebic abscess and hepatitis is abdominal pain (chart 2). This was present in all but one case of amebic abscess. This one case complained of chest pain only. The location of the abdominal pain varies. In the abscess cases, it seems more likely to be localized to the right upper quadrant, as it was in 5 of the 8 abscess cases. One complained of right lower quadrant pain, and the one left lobe abscess complained of left upper quadrant pain. In our cases of amebic hepatitis, the abdominal pain was generalized, epigastric and right upper quadrant in each of 2 cases. One patient complained of right lower quadrant pain. So we can see that except for the fact that abdominal pain is almost always present, the localiza-

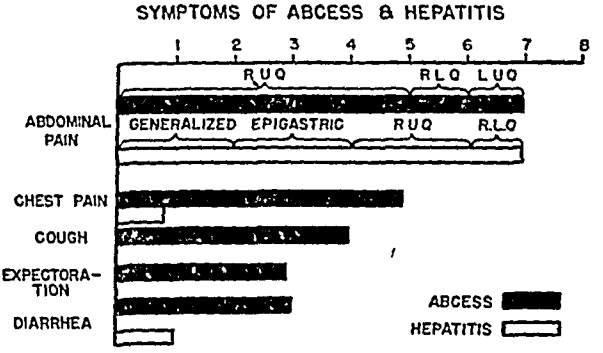


CHART 2

tion is inconstant. The character of the pain is usually dull and aching, but may be sharp and stabbing. It is frequently aggravated by jarring, movement, cough, and deep breathing. These characteristics of the pain were also observed by others (15, 23).

Chest pain is common in the patient with amebic abscess. This symptom was complained of by 5 of the 8 patients. It occurred in 3 cases with thoracic perforation and in two uncomplicated abscesses. It occurs in abscesses of the dome of the liver in which irritation of the diaphragm occurs. One patient with hepatitis complained of chest pain.

Cough was present in 4, or half, of the cases of abscess, but expectoration of muco-prurulent sputum was present only in those cases showing perforation into the thoracic cage. Thus far, the symptoms discussed are non-diagnostic. Diarrhea, because it would call attention to a possible dysenteric disorder, would be an important symptom, but very few of our cases admitted this symptom. Only 3 of the 8 patients with amebic abscess had diarrhea during

the illness, which is an incidence of 37%. Two of these also admitted having had a diarrhea previously, but 5 denied or failed to recall any diarrhea. Only 1 of the hepatitis patients had a diarrhea on admission, but 5 others had had a diarrhea previously. These figures parallel those in the literature where the incidence of diarrhea is reported in 32 to 48% of the patients (2, 15, 20, 21, 23, 31).

Physical findings. Hepatic tenderness and hepatomegaly were universal findings in our group of hepatic complications (chart 3). All 15 cases showed these findings. The liver tenderness could be frequently elicited by palpation and percussion. Tenderness was found in the right subcostal region as well as in the lower interspaces in the axillary region. Intercostal tenderness is usually found when abscess formation has taken place and may point to the favorable site for aspiration. While hepatomegaly was found in all, the liver was palpa-

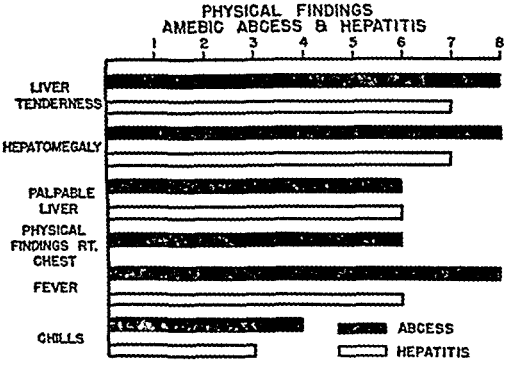


CHART 3

ble in only 12 of the 15 cases. In the other three, the hepatomegaly was demonstrated by the elevated diaphragm.

Abnormal physical findings in the right chest were found in 6 cases. These consisted of dullness, suppressed breath sounds, crepitant râles, and changes in fremitus. True bronchial breathing was not elicited. These findings were of course most marked in the patients with pleuro-pulmonary complications.

Fever was present in all cases of abscess and all but 1 case of hepatitis. The fever was of a septic type showing diurnal variations and frequently went as high as 103 to 104°F. In one-half of the abscess and three of the hepatitis cases the fever was accompanied by chills.

Laboratory findings. Elevation of the right diaphragm was found in all of our cases of hepatic complications (chart 4). This is a very important laboratory finding and is emphasized by many observers (20, 13, 19, 23, 28, 31, 34).

There is no relationship between the degree of elevation of the diaphragm and either the presence of an abscess or hepatitis or the size of the abscess. This differentiation must be made on other grounds. Thus all our hepatitis cases had elevated diaphragms. Some of these were markedly elevated (H.R.S., case 3, fig. 2) while another (W. E. G., case 2), who had the huge abscess, showed at one time no elevation of the diaphragm and later only slight elevation.

X-ray evidence of lung involvement was found in all cases with pleuropulmonary complications and in one case of hepatic abscess. In this latter case, a small amount of pleural effusion was found along the basal atelectasis. In another case x-ray, evidence of atelectasis was found.

An elevated icteric index is an inconstant finding but occurs not infrequently. It was seen in 2 of our hepatic abscesses and 3 of the hepatitis cases, or in $\frac{1}{3}$ of

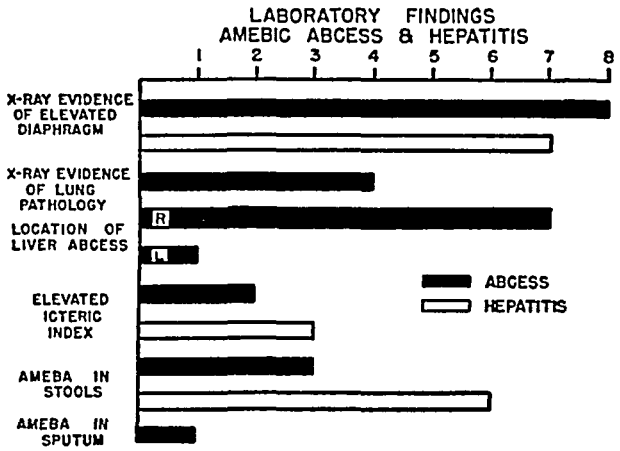


CHART 4

the cases with hepatic complications. However, marked clinical icterus was present only in the large amebic abscess (Case 2, W. E. G.). The incidence of icterus in our cases is higher than that given in the literature. Ochsner (23) gives an incidence of 19 per cent in his cases, Sodeman and Lewis (31) give an incidence of this finding in 15 per cent of their cases.

The finding of amebae in the stools would be of great aid in the confirmation of the diagnosis but unfortunately this was found in a minority of the cases. Only 3 of our 8 cases of amebic abscess showed E. histolytica cysts in the stools, but in the hepatitis cases positive stools were found in 6. This is a high incidence since it is 60 per cent of the total cases. The incidence of positive stools given in the literature is very low, varying between 4.4 and 48.6% (6, 15, 21, 23) Thus it can readily be seen that this finding cannot be depended upon for a diagnosis of extra-intestinal amebiasis. In one of our cases motile amebae were found. The organism was found in the sputum of one case.

The leucocyte count is of some diagnostic help in hepatic amebiasis. The leucocyte count is always elevated, but the elevation is usually moderate. The leucocyte count varied between 13,000 and 21,000 except for 1 case where the count was 28,000 (chart 5). The latter is an exception to the rule that the W.B.C. in amebic abscess of the liver is usually below 20,000, an observation that was made by Ochsner and DeBakey (23). In pyogenic abscesses of the liver, the leucocyte count is usually at the higher level.

The diagnosis of amebic hepatic involvement depends therefore upon an awareness on the part of the physician that this condition is commoner than has heretofore been considered and should be thought of in all febrile conditions in which there is abdominal pain, especially in the right upper quadrant, accompanied by chest symptoms and signs and evidence of hepatic enlargement. If along with this there is exquisite tenderness of the liver, or over the

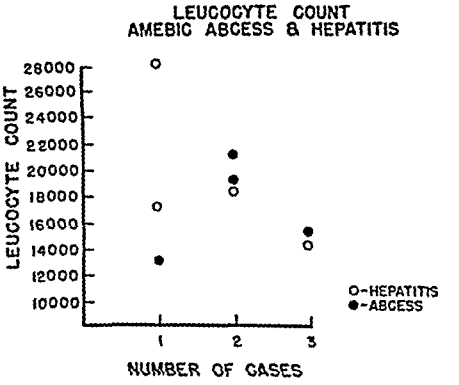


CHART 5

liver area, and in the lower intercostal spaces, and the leucocytosis is below 20,000, a tentative diagnosis of amebic hepatic involvement is in order. A normal leucocyte count or a leucopenia would speak against an amebic liver involvement. Diarrhea, or the finding of the organism in the stools, is an exceptional finding rather than the rule. The absence of the organisms from the stools may be explained on the basis that the intestinal infection may have been eradicated, as was found in our case of cerebellar abscess. An absence of diarrhea even in the past has been explained on the basis of a right sided colon amebiasis in which diarrhea may be absent even in the acute state. It is these right sided infections that are most likely to become complicated by right lobe hepatic involvement, because of the more direct venous drainage from the right colon via the portal vein into the right lobe of the liver.

Treatment. Emetine has gained its reputation as an amebicide because of its

dramatic effect on the hepatic complications of amebiasis. No matter what the pathology in the liver, emetine has a marked and dramatic effect on the symptoms and some of the findings, when given for several days in one grain doses subcutaneously. The fever subsides and the patient feels better. If no large accumulation of pus has taken place, that is if no abscess of any size is present, or there is only a hepatitis, the patient's symptoms may remain under control (Case, H. R. S.). But if considerable pus is present, as in case 2 (W. E. G.), administration of emetine will only cause temporary improvement and only partial disappearance of signs. Tenderness will remain, and the liver will not diminish in size.

Thus, emetine may be a diagnostic as well as a therapeutic agent as has been observed by others (14, 26, 28). The rapid response to emetine indicates that the hepatic disease is due to *E. histolytica*. A rapid recurrence of symptoms, especially fever, indicates the presence of pus and the need for further therapy, such as aspiration.

In addition to the emetine, one of the oral intestinal amebicides are administered to make certain of the eradication of the intestinal parasites.

We are unable to agree with Klatskin's contention that amebic abscess of the liver can be cured completely by emetine alone (14). Large accumulations of prurulent material anywhere in the body is best treated by some form of drainage or evacuation. It would certainly be difficult to conceive how an abscess, like one of ours containing 2,200 cc. of prurulent material, would resolve with emetine alone. There is a two fold danger from continuation of emetine: 1. Emetine is toxic and cumulative and may result in serious damage. 2. Perforation of the abscess with the formation of generalized peritonitis may take place. Therefore, we feel that aspiration with a needle and luer syringe should be done. The place of predilection is in the axillary line over the point of maximum tenderness (22). The procedure is not dangerous and will in conjunction with emetine result in cure of the abscess.

The indications for open drainage are few. The mortality rate with open drainage in a large series of cases was 45.0 per cent while with closed drainage it was only 6.7 per cent (23). Open drainage, however, has to be instituted in patients with left lobe abscess because they cannot be reached safely with an aspirating needle. One of our patients with a left lobe abscess was operated upon and recovered. When multiple abscesses are present, surgical drainage may be necessary but likewise the mortality rises so that when more than 3 abscesses are present, the mortality is said to be 100 per cent (21). This refers undoubtedly to large abscesses because minute multiple abscesses can probably be eradicated by emetine alone.

Our three cases with pleuro-pulmonary complications responded well to

emetine HCl with simultaneous administration of penicillin. In one case, penicillin aerosol seemed to be of great help in resolving the secondary infection.

The two deaths were in patients who received inadequate therapy. One patient died after 7 days of hospitalization. He had a fulminating amebic colitis with several perforations. The other patient died of hepatic abscesses, one of which had perforated with resultant peritonitis, and he also had a cerebellar abscess. It is possible that he may have been saved if he had had aspiration of the liver abscess early in the process.

Intestinal amebiasis and asymptomatic amebiasis, or so-called carriers, should be looked for and treated assiduously. The eradication of the intestinal phase of the disease has a two-fold importance; it will prevent the spread of the disease, and it will prevent the serious complications. We agree with the point of view that amebiasis in any of its stages should be treated adequately. What constitutes adequate therapy of intestinal amebiasis? This question has recently been reopened by the current expressions of the opinion that emetine should be used in all forms of amebiasis, even the asymptomatic states (11, 15). The older observers with more widespread experience are of the opinion that emetine is effective in only a small percentage (35%) of the intestinal form of amebiasis, while the oral amebicides, diodoquin, chiniofon, and carbarsone are effective in as high as 95% of the cases (4, 7, 9, 10, 16, 29). Furthermore, since emetine is a toxic drug, why use it in the face of its ineffectiveness? While emetine is of prime importance in the treatment of extra-intestinal amebiasis, its extensive use in the intestinal form except for the purpose of alleviating the acute dysenteric symptoms is not warranted. There is another point which makes the routine use of emetine impractical. Since 10 to 20% of the United States population is thought to harbor the *E. histolytica* (8, 21), the use of emetine in their treatment would require hospitalization or confinement to strict bed rest, which would affect a large group of patients, rendering this task nearly impossible. The oral amebicides can be used in ambulatory patients and those following their occupations, providing they are not food handlers.

Brain abscess. Amebic brain abscess is a very rare but invariably fatal complication of amebiasis. Craig (4) mentions that only 53 cases have been reported in the literature, only one of these being in the cerebellum. Thus, ours becomes the second case of cerebellar abscess reported in the literature. This complication usually occurs secondarily to liver abscess, as occurred in our case. Most of the patients with brain abscess have been between 20 to 40 years of age (33), our case with this complication was 40. The belief is expressed that traumatization of a liver abscess may be the cause of brain extension. Since this has always been an invariably fatal complication, more effective treatment of the earlier stages of amebiasis is necessary to prevent this complication.

SUMMARY AND CONCLUSIONS

1. The experience with amebic colitis and its complications in veterans of World War II is reported.

2. There appears to be an increase of the incidence of active, virulent amebiasis in veterans of World War II. There is a relationship between the exposure in tropical climates and the incidence of the disease.

3. Fifteen cases of hepatic complications were observed in a group of 58 cases, showing a high incidence of these complications, which is indicative of a virulent infection.

4. The treatment of choice for hepatitis is emetine, and for hepatic abscess, emetine plus aspiration.

5. The wisdom of using emetine in carriers is doubted, and we are in agreement with the opinion that the intestinal amebicides produce excellent results and are without danger. They do not require hospitalization of the patient.

6. One case complicated by a cerebellar abscess is reported, which is the second case found in the literature.

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DESCRIPTION OF GASTROSCOPIC APPEARANCE OF LUETIC GASTRIC LESIONS IN LATE ACQUIRED SYPHILIS[1]

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Andral (1) described the first two cases of gastric syphilis in 1834, and there were many reports of the disease in the following decades. But gastric syphilis has been proved etiologically (2, 3), and its pathology (4, 5, 6, 7) and incidence (8, 9) have become well recognized only in recent years. Although the stomach is the most frequent site of gummatous lesions in the gastrointestinal tract, gastric syphilis is nevertheless rare, occurring in 0.3% of all patients having syphilis (10), 4% to 8% of all syphilitic patients having "stomach trouble" (8, 9). Eighty-nine gummatous gastric lesions were found in 25,000 syphilitic patients (6). Thus it is evident that in the syphilitic patient an obstructing lesion in the lower third of the stomach is more likely to be carcinoma than ulcero-nodular syphilis, or an infiltrating lesion more likely scirrhous carcinoma than leather bottle stomach of syphilis. Syphilis of the stomach seems moreover to be a "disappearing" disease (11) but nevertheless we doctors are now not infrequently confronted with gastric lesions in the patient who harbors late acquired syphilis, emphasizing the need of our ability to differentiate these lesions with minimum indecision or delay.

The clinical syndrome of gastric syphilis is not strictly pathognomonic in that symptomatology often suggests benign ulcer whereas the low or absent gastric acidity and the roentgenologic appearance may suggest carcinoma (12, 13, 14). Often most helpful are the history and physical findings, the average age of thirty-five years, weight loss, or the positive serologic tests for syphilis. In brief, the over-all picture to the experienced clinician provides the correct diagnosis in about 75% of instances (12, 15). The lesions in the stomach are variably ulcerative, ulcero-nodular, nodular, infiltrative, or fibrosing (12), and may involve only segments, usually the lower third, or may involve almost the entire stomach. The pathology in late acquired syphilis of the stomach is most evident about the vessels of the submucosa, an invasion of lymphocytes and plasma cells along the perivascular lymphatics, into the vessel walls, finally producing an intimitis, obliterative periendophlebitis (5) and arteritis—a panvasculitis of the submucosa. There is a variably thickened, fibrosed submucosa (16, 17) with a shallow, often large, branching necrotic ulcer of the mucosa (18), even in the absence of free hydrochloric acid. Such lesions lose their

[1] Read at the meeting of the American Gastroscopic Society, Atlantic City, New Jersey, June 8, 1947.

activity, color, and morphologic characteristics "long before the patient reaches the autopsy table" and usually within a few days after beginning antiluetic therapy. In contrast, the *untreated* gumma of the stomach is recognizable without difficulty by the pathologist or experienced surgeon at the operating table (19).

That gastroscopy in some instances offers help in the identity and progress of treatment of these gastric lesions of late acquired syphilis has been described, along with carefully detailed clinical data including biopsy and resected specimens, by some of our foremost gastroenterologists during recent years (5, 18, 20, 21, 22, 23).

Our 14 patients studied gastroscopically and having clinically proved *and untreated* gastric syphilis were from a total of 16,714 patients having positive serologic tests for syphilis during a period of several years in a city where "health cards" are required of certain groups as, for example, domestic help and food handlers. These patients were seen in the outpatient gastrointestinal clinics of Parkland (Dallas City-County) Hospital, of Baylor University Hospital, and in our office. Following admission to the medical services of these hospitals, *specific treatment was withheld* in an effort to get adequate studies, including radiologic and gastroscopic studies, of the untreated stomach lesion. Roentgenologic diagnoses and followups were done with the greatest of interest by Drs. Palmer Wigby, J. R. Maxfield, Jr., and A. J. McIlwain of the Department of Radiology, Southwestern Medical College, and Parkland Hospital. Four patients were operated upon by Drs. Sam Weaver, Robert Short, John V. Goode, and Walton Cochran, all of the Departments of Surgery of Parkland and Baylor University hospitals and of the surgical staff of Southwestern Medical College.

For antisyphilitic therapy, these patients were under Dr. Arthur G. Schoch, chief syphilologist of the Venereal Disease Clinic and Penicillin Center. One patient, L. J., could not be located after becoming symptom free. Although inadequately treated, he had one of the most strikingly characteristic, large, shallow, multiple, ulcerating lesions of the lower third of the stomach which disappeared to x-ray and gastroscopy after only 6 weeks of antiluetic therapy. Otherwise the patients were followed by x-ray and gastroscopy for 18 months to 9 years. Twelve of these patients previously reported (24) are included herein because of an additional 5 year followup.

The gastroscopic efforts can be evaluated best by presenting the essential findings in four patients.

CASE REPORTS

Case 1. White male, aged 47 (laborer), was admitted to Parkland Hospital November 1, 1940, with chief presenting symptoms of 5 weeks' epigastric fullness and

pain after meals, relieved by vomiting undigested food, with weight loss of 8 pounds in 3 months. His history revealed gonorrhea and a "chancre" which healed with home treatment 19 years before. Physical findings as follows: white male appearing older than stated age, fair nutrition, blood pressure 100/60, no unusual adenopathy, heart essentially normal, 2 plus tender epigastrium, no abnormal masses. Working diagnosis: "Gastric carcinoma." Gastric analysis after histamine: free HCl 0°, combined acidity 10°. Repeated blood Wassermann, Kahn, and Kline positive. Blood counts and blood chemical analyses were done in contemplation of operation, with essentially normal findings. X-ray diagnosed "large ulcerating lesion, lesser curvature, lower third of stomach." Gastroscopy visualized a large ulceration of the greater curvature opposite the incisura angularis. The ulcer base appeared shallow, smooth gray surrounded by irregular and serpiginous mucosal borders presenting segments of circles off the main ulcer. The mucosal margins were of slightly livid or purplish red color.

Gastroscopic diagnosis: "large ulcerating lesion, lower third of stomach, probably carcinoma. Syphilitic ulcer cannot be excluded."

At operation by Dr. Sam Weaver "there were numerous glands along both lesser and greater curvatures, the liver and pancreas appeared normal, and a large area of velvety feel in the distal third of the stomach was noted, with practically no induration. About two-thirds of the stomach and one inch of duodenum was resected, and continuity of bowel reestablished by method of Billroth I." Preoperative diagnosis: "Carcinoma of stomach." Postoperative diagnosis: "Luetic ulcer of stomach."

Tissue report: "Grossly a large shallow ulcer 6 by 1.8 cm. with smooth base, serpiginous serrated edges with mucosal borders not elevated." Section showed "ulceration of glandular lining epithelium with no neoplastic change." The ulcer floor was composed of granulation tissue infiltrated by neutrocytic, lymphoid, and plasma cells. The mucosa showed infiltration of lymphoid and plasma cells. The submucosa was markedly thickened by a granulative tissue in which were infiltrating lymphoid, plasma, and eosinophilic cells. Perivascular lymphoid and plasma cell infiltrations were present. Elastic tissue stain showed a marked endophlebitis and panphlebitis in the submucosa. Diagnosis: "Chronic benign ulceration of stomach—syphilitic origin possible." (13) The patient continued his treatment and followup in the Venereal Disease Clinic three and one-half years.

Case 2. Colored female housewife, aged 29, admitted to Parkland Hospital medical service of Dr. Grady Reddick May 19, 1938, with chief presenting complaint of 2 years' indigestion, weight loss of about 50 pounds (present weight 83 pounds), cramping epigastric pain followed by much vomiting for 7 or 8 weeks.

Physical examination revealed a palpable mass verified later by Dr. Palmer Wigby's fluoroscopy and plates to be "extensive involvement mid-half of stomach due either to carcinoma, polypoid type, or to syphilis of the stomach." Repeated blood Wassermann, Kahn, and Kline were positive.

Gastric analysis: no free hydrochloric acid, combined acid 16.8°.. Repeat fractional test meal after histamine revealed no free hydrochloric acid.

At gastroscopy June 1, 1938 the scope met resistance and could not pass into the lower segment of the stomach. A large, red, smooth prominence was noted on the posterior wall and lesser curvature. The mucosa over the tumor margins was grayish, and blood vessels coursed over these margins. There was atrophic mucosa throughout the stomach. Gastroscopic diagnosis was (1) large, smooth, tumor-like prominence in the mid-stomach compatible with malignancy or possible granulomatous lesion of syphilis; (2) extensive atrophic gastric mucosa.

Antiluetic therapy, bismuth grs. iii intramuscularly was started May 19. Reexamination in X-ray June 3, 1938 revealed "oral barium again demonstrates deformity in mid-third of stomach. Peristaltic waves appear to pass and the rugae appear uninterrupted, with disappearance of palpable mass." On June 17, "no 6 hour retention; definite decrease in deformity mid-third, and peristalsis passes through the entire stomach satisfactorily."

Recheck gastroscopy July 20, 1938 (after 2 months of antisyphilitic therapy) revealed (1) view of lower segment of stomach obstructed by spasticity or tumor in the middle third; (2) atrophic gastric mucosa.

Recheck gastroscopy September 21, 1938 (after 4 months of antisyphilitic therapy) revealed the following: the gastroscope met with no undue resistance and the entire stomach, including the pylorus, seemed to be visible. At the site of the former tumor the mucosa appeared mottled white and pale pink with visible red blood vessels coursing through the area. The rugae were absent in this area and very little in evidence elsewhere in the stomach although regular peristalsis was seen and the pylorus appeared to open and close normally. At this time, and again October 15, 1941, gastroscopic diagnosis was: (1) atrophic gastric mucosa; (2) at the site of the healed gumma of stomach there is mottled white mucosa. The patient had gained from 83 pounds to 138 pounds during the 3 years and 4 months of observation.

Case 3. Colored male, aged 36, farm laborer, admitted to Baylor University Hospital January 3, 1939 with chief presenting complaints of "chronic indigestion worse after meals, more recently relieved by lying down or vomiting." Weight loss of 44 pounds from former weight of 115. History of gonorrhea as a youth and repeatedly since, the last attack having been 2 years previously. Patient said he had had a "chancre" when a young man.

To physical examination, there was an emaciated colored male but no localizing stigmata of syphilis except scars on shaft, coronary sulcus, and glans penis. Blood pressure was 106/74.

Gastric analysis revealed free hydrochloric acid 5°, total acid 30°. Blood Wassermann, Kahn, and Kline were repeatedly positive.

X-ray by Dr. J. R. Maxfield, Jr. on January 5, 1939 revealed a small high stomach with very spastic, narrow antrum "compatible with benign ulcer with marked spasm and contracture. Very little emphasis on carcinoma."

Gastroscopy January 20, 1939 revealed absence of normal rugae—mottled, edematous, infiltrated appearing stomach. The pylorus could not be seen apparently because of marked spasticity of the stomach.

At operation January 23, 1939, Dr. John V. Goode reported the findings in the stomach. Cut section revealed in the lower third of the stomach wall a markedly thickened submucosa—"thicker than the emaciated (73 pound) patient's abdominal wall." Posterior gastro-enterostomy was done. The surgical diagnosis was that of syphilitic fibrosis of the stomach, and the patient was accepted by the Venereal Disease Clinic for treatment of "gastric syphilis."

Gastroscopy was repeated in 6 months, June 2, 1939. The stomach was very spastic, retained the air poorly. The surgical stoma was observed open, and brownish Kerkring folds of jejunum appeared normal. There was no evidence of ulceration about the surgical stoma. The stomach wall presented large folds and absence of normal rugæ. The picture was considered compatible with luetic, infiltrative, leather bottle stomach. This patient gained 35 pounds and was followed in the Outpatient Department for 3 years 8 months, still not well nourished but ambulatory, compatible with the permanent changes and malfunction of syphilitic fibrosis of the stomach.

Case 4. Colored male, laborer, aged 42, was admitted to Parkland Hospital medical service of Dr. Edwin Rippy March 18, 1940 with chief presenting complaints of 10 weeks' abdominal pain relieved by vomiting and without relief during 3 months on ambulatory ulcer regime in Outpatient Clinic. Venereal Disease Clinic history states probable duration of syphilis as 20 years.

Physical examination revealed an emaciated colored male with blood pressure of 110/74, and essentially negative findings except for epigastric tenderness and rigidity.

Blood Wassermann, Kahn, and Kline were positive. Gastric analysis after histamine March 19, 1940 disclosed free hydrochloric acid 0°, combined acid 12°; occult blood was positive in stool.

X-ray March 19, 1940 revealed "a large prepyloric lesion which was extremely tender. No palpable mass. Impression: probable large ulcerating carcinoma—suggest short course of antiluetic therapy if Wassermann positive."

Recheck x-ray April 11, 1940: "There is less gastrospasm and the tenderness has completely disappeared . . . Antiluetic treatment, however, may show similar improvement of a gastric carcinoma."

Gastroscopy March 20, 1940 revealed a large, irregular ulceration on the anterior wall below the angulus; grayish green exudate covered the base; there was some nodulation of adjacent mucosa. The appearance suggested neoplasm. Luetic lesion could not be excluded.

Antiluetic therapy, bismuth and neoarsphenamine, was continued from March 19, 1940.

Gastroscopy March 27, 1940 revealed "less infiltration about the ulcer. It appears more benign and peristaltic waves pass uninterruptedly."

Gastroscopy April 10, 1940 revealed "no remaining ulceration."

On April 13 this patient was discharged to Outpatient Department and Venereal Disease Clinic. Clinical diagnosis: "Luetic ulceration of the stomach." Patient recovered symptomatically.

Gastroscopy May 1, 1940 revealed a narrow appearing antrum. A good view revealed no ulceration and apparently normal flexibility. There appeared to be satisfactory healing of the ulcer noted at the time of the first two gastroscopies.

Gastroscopy August 7, 1940 revealed regular peristalsis and normally glistening mucosa throughout the stomach, with no visible lesions.

X-ray recheck May 1, 1940, August 7, 1940, May 2, 1941, June 20, 1941 by the same radiologist, Dr. P. E. Wigby, while the patient continued antisyphilitic treatment in Venereal Disease Clinic, showed "all negative for upper gastrointestinal lesion."

This lesion was the ulcero-nodular type. The livid, purplish red color of the ulcer margin was not mentioned in any gastroscopic reports.

It was after this patient and the ulcerating lesion (Case 1) were studied that a patient with gumma of the palate (14) came to the clinic. This lesion called to mind other gummas of the palate, and the striking resemblance to syphilitic ulcerating lesions in the stomach was noted. Worthy of special mention it seems is a livid or violaceous, slightly brownish or purplish red hue of the irregular, serpiginous, mucosal margins of these large, shallow, ulcers. Stokes (14) has stated: "Perforation of the hard or soft palate is the nearest approach to a pathognomonic sign of syphilis to be found on the mucous membranes." It is our impression that the ulcerating gumma of the stomach thus has a *gastroscopic appearance* which also approaches a pathognomonic sign of syphilis.

The appearance of the blood vessels coursing over the edge of the gummatous tumor in Case 1 was noted and has been described elsewhere (4, 19, 25).

Gastroscopic studies of the leather bottle stomach have been well described in the literature (18, 20, 21, 22) and were presented also in Case 2 above.

Five other patients having ulcerating lesions of the stomach and fulfilling the requirements of the clinical syndrome of syphilitic etiology were studied gastroscopically. One single, round ulcer was studied on the greater curvature in a colored male, aged 34, who had been treated for syphilis 4 years previously. There had been a palpable mass producing x-ray deformity of the stomach, which disappeared on antiluetic therapy. He had discontinued therapy as soon as he felt better, then returned 4 years later with the ulcer which we had opportunity to study gastroscopically. He had no relief from rather continuous pain after 3 weeks of peptic ulcer management. His ulcer was on an elevation (19) and presented the violaceous color of the mucosa about a necrotic base. The lesion had disappeared when x-ray examination was carried out following 4 weeks of specific antiluetic therapy, and at 6 weeks it could no longer be seen by gastroscopy.

SUMMARY

In 14 patients, the lesions appeared to be those of ulcerating and ulcero-nodular syphilis of the stomach in 8, nodular or gummatous tumor without ulceration in 3, and infiltrative or leather bottle stomach of syphilis in 3 patients.

The livid or slightly brownish to violaceous color of the mucosal margins of

the ulcers, the ulcer being at times "as large as a child's hand," seems to have as a pathologic basis, a fibrosing, obliterating panvasculitis of the submucosa. The ulcer would seem to occur just as ulcers occur in gumma of the skin or palate. In the absence of free HCl, it is probably not a peptic ulcer but is a necrotic ulcer, the result of deprivation of its normal blood supply. Should earlier luetic lesions than the ulcerating gumma be discovered in the stomach, the lesion would no doubt be more vascular. In one patient previously reported by us (24, Case 11), there was hematemesis, and hemorrhagic erosions seen in the antrum at gastroscopy were proved by section to be those of the luetic lesion appearing not as yet deprived of its blood supply. Whereas, in the cases having luetic ulcerating lesion there appeared to be more chronicity, more submucosal fibrosis, and comparatively less vascular mucosal margin of the ulcer. To gastroscopy, a livid hue of the mucosal margins about the luetic ulcer thus appears somewhat different in color from the often comparatively normal pink color of gastric mucosa about a peptic ulcer or the fiery red, highly vascular margins of an ulcerating carcinoma of the stomach.

We have presented the description of the gastroscopic appearance of *untreated* gastic syphilis in the ulcerative type, the ulcero-nodular type, the large nodular or tumor type producing hourglass stomach, and the infiltrating, fibrosing or leather bottle type, together with related data and followup gastroscopy before and during antisyphilitic therapy. It is intended to emphasize that the livid, purplish or brownish red or violaceous color of the serpiginous mucosal borders about a large, irregular, shallow ulcer may be of help in the gastroscopic identification of luetic ulcerating lesions of the stomach in late acquired syphilis.

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DISCUSSION ON PAPERS ON GASTRIC SYPHILIS

BY DR. I. R. SCHWARTZ AND DR. C. O. PATTERSON

(Dr. Schwartz's paper appeared in the February issue of Gastroenterology)

DR. J. T. HOWARD (Baltimore, Md.): When I was asked to discuss the papers of Dr. Schwartz and of Dr. Patterson I felt thoroughly unfitted to do so, for, to my knowledge at that time, I hadn't examined gastroscopically a single case of syphilis of the stomach. I had agreed with J. E. Moore in the belief that the "stomach trouble" of syphilitics was rarely caused by gastric lues. Since gastric syphilis is so extremely uncommon, at least as a tertiary manifestation of the disease, I knew that I couldn't expect to find two or three cases for gastroscopy by soliciting them from the syphilologists in the few weeks before this meeting. Therefore, I had the record room of The Johns Hopkins Hospital get out for me the histories of patients in whom the diagnosis of gastric lues had been made and I also reviewed the cases listed as syphilis of the stomach in the file of the Clinic for the Study of Syphilis. In all, the diagnosis had been made with reasonable certainty in 20 of 33 cases in the twenty-four years from 1923 to the present. To my surprise, I found that *I* had made endoscopic examinations on 2 of these patients. One *certainly* had secondary syphilis and the other *probably* had a tertiary luetic lesion in the stomach.

The first patient was a colored man, thirty-four years of age, who in June of 1940 acquired a penile sore. Two months later he began to vomit and he lost 26 pounds. Because of these symptoms, he came to the Dispensary of The Hopkins in September of 1940. There a mass was noted in his epigastrium, the S. T. S. was positive, and skiagrams showed a flexible deformity of the lower end of the stomach which was thought to be caused by external pressure; there was some degree of pyloric obstruction. I had been requested to make a gastroscopic examination and I had recorded that I had found a distensible, reddened stomach with peristalsis present in the antrum. The mucosa seemed to be edematous and one small erosion was seen. I told the staff of the presence of gastritis and I said that I could find no gastroscopic evidence of neoplasm. I didn't think of the possibility of gastric lues. The patient was treated with arsenic and with bismuth and with iodides from September to November fifth, when his abdomen was explored by the surgeons because his clinical improvement had not been striking and because of persisting gastric deformity. At

the laparotomy the gastric wall was 8 mm. in thickness at the lower end of the stomach and there was such tremendous enlargement of the lymphatic nodes about the pylorus that some obstruction had been produced. Biopsy of the gastric wall showed chronic perivascular inflammation which caused the pathologist to write the microscopic diagnosis of syphilis of the stomach. A lymphatic node was labeled by him as showing hyperplasia. Both the medical and surgical services wrote the diagnosis as syphilis of the stomach and I might modify that by specifying secondary gastric syphilis.

The second patient in whose case gastric syphilis was a probable diagnosis and on whom I made an endoscopic examination was a negress of 55 years who was admitted to The Johns Hopkins Hospital February 21, 1942, and who remained there only until March 11 of that year. At the time of her discharge the diagnosis of the resident staff was carcinoma of the stomach, latent syphilis, and nodular non-toxic goitre. This woman had 10 living children and one other child had died in infancy. About May of 1941 she had begun to have some epigastric discomfort after meals; her appetite remained good and she reduced her intake of food only because of the discomfort resulting from eating. By Christmas of 1941 she had begun to have dysphagia on taking solid food and she would induce vomiting for relief. In three months she lost from 120 to 104 pounds. At her physical examination there was a suggestion of the presence of an epigastric mass. The S. T. S. was positive. Roentgenograms showed a widely dilated esophagus with smooth obstruction at the cardia and the radiologic diagnosis was achalasia. I made an esophagoscopic examination which was essentially negative. However, I had been unable to introduce the 'scope into the stomach. The late E. B. Freeman wanted to dilate the stricture but he could not get the patient to swallow a thread and we were not then using weighted dilators. The patient was sent up for surgical exploration and at the operating table the surgeons could feel a "cancer-hard mass" involving the upper third of the stomach and extending to the esophageal orifice. There were a number of "carcinomatous glands" around the head of the pancreas and along the aorta and high on the lesser curvature of the stomach. None of these could be removed easily and no tissue was taken out. The liver appeared to be all right. A gastrostomy was done and on the day that the patient left the hospital the stomach was filled with barium through the tube and barium was given by mouth. Films were read as showing no evidence of an organic lesion in the gullet or in the cardiac end of the stomach; no signs of external pressure on these organs were noted. Treatment of the patient's syphilis was advised just because the presence of cancer had not been definitely proved and she returned to her home in Virginia. How much anti-luetic treatment she really had is not known. On November 16, 1946, four years and eight months after her operation, a letter was sent to her physician saying in part, "We are very anxious to know the patient's condition, if alive, or, if not, the date and cause of her death." He replied, "D. B. is alive and well. Rather too much weight. Does not have any symptoms of her pre-operative condition." So the diagnosis of gastric cancer must have been wrong; the diagnosis of gastric syphilis is presumptive; that of cardiospasm is possible.

My examination of the records of the 33 patients with possible or probable gastric syphilis has made me feel that the diagnosis is not an easy one to make in a short period of observation; the clinical diagnosis is often presumptive and microscopic proof is most desirable.

The essayists this morning have done us a scientific service by reporting their gastroscopic observations in stomachs presumably affected with luetic disease. However, while I shall pay a great deal of attention in the future to what I see through endoscopes in examining patients who *may* have gastric syphilis, I shall be reluctant to make the gastroscopic diagnosis of a luetic stomach on patients over 40 who may be referred to me for gastroscopy only. Cancer is so much more common and the differential points noted gastroscopically aren't too sharp.

In the early days of The Hopkins Professor Halsted liked to go through elaborate and brilliant differential diagnoses before his operations and he, always looking for rare diseases, would frequently diagnose them pre-operatively. Dr. J. M. T. Finney, his first lieutenant and a very practical man, would bet on the probabilities in commenting on the cases diagnosed by Halsted and he was proved to be correct more often than the Professor. At one time when this happened, Halsted made his famous remark, "Finney, the best diagnosis is not always the correct diagnosis."

Let us not yet lean too heavily on the gastroscopic evidence of syphilis of the stomach. 'Tis a bit fancy for me and, even with the help of such careful observations as have been reported to us this morning, I believe that it is safer for the reputation of gastroscopy if we are Finneys more often than we are Halsteds when the possibility of a luetic lesion of the stomach comes to our minds at endoscopy.

DR. ROY LYMAN (Washington, D. C.): Dr. Schwartz mentioned a report which I presented about ten years ago, describing the appearance of the gastric mucosa in over one hundred cases of secondary lues. Perhaps this audience might be interested in knowing the purpose for which that study was done and what, if anything, was gained as a result.

Some years ago, when I was studying under Dr. Moutier, I asked the professor to describe the characteristic appearance of syphilis of the stomach. He said he did not know and that he had had too few cases to draw any definite conclusions. Many years later I asked Dr. Schindler the same question and he replied that he, also, did not know.

I then set out to find out where the greatest number of syphilitic patients were treated and was referred by the U.S.P.H. to Hot Springs, Arkansas where the large V.D. Clinic is located. With the greatest cooperation of the clinic, one hundred and thirty selected cases were gastroscoped and at this moment we are still attempting to evaluate the findings.

Certainly a large number of syphilitics will have the infection invade the stomach wall. The pathology that follows may be drastic and extensive, or mild and variable, depending on the degree of infection and the length of time the organism remains in the peri-vascular lymph spaces in the gastric mucosa. Almost any kind of infiltrative tissue pathology may follow this invasion and the surface appearance of the mucosa

will probably never present an entirely characteristic appearance. In all probability, the greatest damage can come from the connective tissue replacement after the infection has been cleared up. This will give the gastroscopist the most frequent appearance, that of the leatherlike, plastic stomach resulting from an increase of cicatricial tissue.

I think the present discussion of the gastroscopic appearance of syphilis of the stomach is very timely. In most cases, it is extremely difficult to determine by appearance alone, a differential diagnosis of syphilitic ulceration, as well as gummatous enlargements which simulate adenomas.

A recent case illustrated this. A middle aged woman presented a large, elevated adenoma on the greater curvature. Wasserman in this case was four plus. Under luetic treatment, X-ray showed the tumor to decrease in size slightly. Nevertheless, the X-ray department believed this to be a carcinoma, the attending physician believed it to be a syphiloma. The gastroscopic appearance was not characteristic enough to make a diagnosis. The surgeon resected the tumor, the gross appearance left the diagnosis in doubt, finally the pathologist reported a tuberculoma.

DR. BROWNE, (New Orleans): There are just two comments I wish to make. I feel Dr. Patterson should be congratulated on his consistency. After hearing his first presentation on this subject some five years ago I felt I could return to Charity Hospital in New Orleans and confirm these observations quickly. Yet in these intervening years I have observed only two lesions gastroscopically which might fit this picture, and I regret I missed the diagnosis in both instances. The first proved a benign peptic ulcer at surgery. In the second case I rendered an opinion of tuberculosis with which I was working experimentally at the time, and of course, was hopeful of finding. This lesion later proved to be luetic. However, I am accepting Dr. Patterson's criteria, but I must stress the rarity of the lesions and difficulty in recognition. The second comment is the gastroscopic picture described by Dr. Schwartz. This is quite similar to what we have observed in acute exanthematous disease, particularly scarlet fever, and I am wondering if the mucosal changes might not be accounted for on the toxic basis.

DR. MICHAEL WEINGARTEN (New York): Both Dr. Patterson and Dr. Howard have pointed out the difficulty encountered in the differential diagnosis between carcinoma of the stomach and late syphilis of the stomach, and I think it is particularly in that situation that gastroscopy can be of great value. Many of the reported cases of syphilis of the stomach show a concentric narrowing of the distal portion of the stomach with absent peristalsis and the radiological diagnosis in these cases is usually carcinoma of the stomach. This was true of a case which Dr. Rafsky and I observed recently, a forty-nine year-old man who had a positive serology and a history of severe epigastric pain, complete anorexia and showed a weight loss of forty pounds. Gastroscopically, there was no question that we were not dealing with a diffuse lesion of the distal half of the stomach. There were five nodular elevations, 0.5 to 1 cm. in size. Adjacent to one of them there was a shallow ulceration, but

otherwise the intervening mucosa was perfectly normal. We were able to observe the shrinkage in size of these nodules and their ultimate disappearance under antiluetic therapy. The ulceration also healed completely.

I think that in a case where nodular infiltrations of the gastric mucosa and shallow ulcerations are observed, with a good symptomatic response and gastroscopic observation of the disappearance of nodules and ulcerations with antiluetic therapy, one can unhesitatingly make a diagnosis of late syphilis of the stomach.

I would like to mention just one aspect of treatment, and that is a caution which Dr. Bockus has pointed out, namely, the danger of giving these cases arsenicals and iodides in the early stages of treatment. He reported a case of perforation where iodides were used. The treatment should be started with Bismuth.

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THE EFFECT OF DIETARY FAT ON FECAL FAT EXCRETION AND SUBJECTIVE SYMPTOMS IN MAN[1]

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Available evidence regarding the effect of the quantity of dietary fat upon that of fecal fat is difficult to interpret. This is due to the fact that no studies have been reported in which the same subjects were given isocaloric diets containing various amounts of a specified fat. Disregarding variations in caloric intake, differences in types of fat, the poor distribution of subjects, and using the average fecal fat values when the diet contained 15 to 350 grams of fat, analysis of data from various sources (1–14) reveals a statistically significant correlation (0.65) between fat intake and fat excretion.

Three subjects studied by Atwater and Benedict (1, 2) received 2500 to 5500 calorie diets, each containing different amounts of fat. The high calorie diets were associated with high values for fecal fat, regardless of the fat intake. There was no significant increase in fecal fat as the dietary fat was increased at isocaloric levels.

The present study investigates the relationship between fat intake and fecal fat excretion when 40 subjects are given two types of fat at three levels, and the daily caloric intake remains at 3000.

METHODS

The dietary experiment. Forty medical and dental students were studied in groups of 10 for six weeks each. The subjects ate all meals, prepared by the same dietitian throughout, in a special dining room reserved for this study. The first week of the test the subjects in Group I were given daily 3000 calorie diets which included 60 grams of lard used in the preparation of the food. The second week the menu was repeated, except that 60 grams of hydrogenated vegetable oil (HVO—"Crisco") were used. Similarly, during the third and fourth weeks the daily diet contained 120 grams of lard and HVO, respectively, and during the fifth and sixth weeks 150 grams of lard and HVO, repsectively. This schedule was rearranged for the subjects of Groups II, III, and IV, so that each group began with a different fat level. In Group IV the 120 gram level of added fat was omitted.

The menus at the various fat levels are given in Table I. The composition of the meals and of the added fats are given in Table II.

[1] Aided by a grant from the American Meat Institute, Chicago, Illinois.
[2] Now at the University of Illinois, Chicago.

The weekly diet periods began on Monday morning. The subjects collected their feces from noon on Tuesday through noon on Sunday. The specimens were preserved in tightly-capped quart jars containing 100 cc. of 95 per cent ethyl alcohol. Specimen jars were placed in a refrigerator daily.

TABLE I

Menus at three levels of dietary fat

	60 GRAMS ADDED FAT	120 GRAMS ADDED FAT	150 GRAMS ADDED FAT
Breakfast:			
Fruit juice	200	200	200
Cereal	30	30	30
Bread	40	40	40
Eggs	120	120	120
Milk	240	240	240
Preserves	30	20	20
Added fat (lard or HVO)*	20	43	53
Lunch			
Fruit juice	160		
Turkey, chicken or salmon	100	100	100
Potatoes	75	75	
Tomatoes or beans	100	100	100
Bread	40	40	30
Preserves	25	10	10
Milk	240	240	240
Canned fruit	160	130	100
Added fat (lard or HVO)*	20	39	49
Dinner			
Fruit juice	200		
Dried beef or hamburger	100	100	100
Potatoes	75	75	
Corn or carrots	65	45	75
Bread	40	40	30
Preserves	15	10	10
Milk	240	240	240
Canned fruit	140	110	150
Added fat (lard or HVO)*	20	38	48

* Added lard or HVO colored and flavored as spread for bread, or incorporated into meal.

Fecal analyses. Five-day stool specimens were homogenized in a Waring blender. Two methods of total fat extraction were used. One was a modification of the Saxon wet extraction method described by Hawk and Bergeim (15). The second method was the dry extraction technique of Fowweather and Anderson (16). Both methods were found to have reliability coefficients of 0.98 upon duplicate extractions and upon analyses of known samples. Fecal samples analysed by the two methods did not differ significantly.

Free fatty acids were determined as described by Fowweather (16). The iodine numbers were determined after Hawk and Bergeim (15). Kjeldahl nitrogen determinations were made on five-day pooled samples.

Statistical evaluation of all data was made by the method of analysis of variance (17). Intraclass correlation was used as a measure of the reliability of the various determinations.

TABLE II

Composition of daily meals

	60 GRAMS* ADDED FAT	120 GRAMS* ADDED FAT	150 GRAMS* ADDED FAT
Total calories, calculated	3000	3000	3000
Grams total fat by analysis	93.4	139.7	167.5
% fat of wet weight of meals	4.3	6.3	8.4
% fat of dry weight of meals	18	27	39

Composition of added fats†

	LARD	HYDROGENATED VEGETABLE OIL
Iodine number	64.5–65.8	72.6–74.2
Melting point	41.6°C.	43.8°C.
% Free fatty acids	0.38	0.13

* Lard or hydrogenated vegetable oil (Crisco).

† Analyses by Swift and Co., Wilson and Co., and Armour and Co., Chicago, Illinois.

TABLE III

Summary of effect of dietary fat on fecal fat excretion

TOTAL DAILY FAT INTAKE	LARD OR HVO INCLUDED IN DIET	MEAN DAILY TOTAL FECAL FAT, (5-DAY SAMPLES)	
		HVO	Lard
grams	*grams*	*grams*	*grams*
93	60	4.33	3.75
140	120	3.60	3.90
168	150	3.75	4.10

Difference in means necessary for significance (.01 probability) = 0.71 grams*.

* Derivation of this term is given in table IV.

RESULTS

Total fecal fat excretion. The mean daily total fecal fat excretion based on five-day fecal samples for the forty subjects are summarized in Table III.

It is evident that neither the quantity nor type of ingested fat influenced the quantity of fat excreted in the feces. The detailed individual results are given in Table IV together with a summarized statistical analysis. There were highly significant differences in fecal fat excretion between subjects. These differ-

TABLE IV

The effect of dietary fat on fecal fat excretion

Average daily total fecal fat, in grams

SUBJECT	60 GRAMS ADDED FAT		120 GRAMS ADDED FAT		150 GRAMS ADDED FAT		SUBJECT	60 GRAMS ADDED FAT		120 GRAMS ADDED FAT		150 GRAMS ADDED FAT	
	HVO	Lard	HVO	Lard	HVO	Lard		HVO	Lard	HVO	Lard	HVO	Lard
1	5.9	6.3	4.1	5.2	7.7	6.0	21	4.1	2.9	1.7	1.8	3.3	3.2
2	4.1	3.5	4.1	4.4	4.2	4.7	22	1.5	5.1	2.2	5.8	2.8	4.7
3	2.2	2.3	2.3	2.4	2.6	1.5	23	5.8	2.2	2.4	3.2	3.3	3.7
4	4.9	5.3	5.3	4.1	3.8	5.3	24	4.9	2.7	3.9	1.8	3.7	2.5
5	3.2	2.5	1.6	3.5	3.2	2.8	25	4.7	5.9	4.9	5.2	2.5	2.4
6	2.9	2.5	2.0	4.2	1.6	3.7	26	2.7	2.5	3.0	3.1	2.6	3.7
7	3.6	2.4	2.3	4.0	3.0	6.3	27	6.8	3.6	3.1	3.2	2.92	2.1
8	1.8	1.8	3.7	3.6	4.7	3.6	28	10.4	2.1	5.3	5.2	0.8	3.3
9	4.0	3.7	4.7	4.3	5.9	5.4	29	3.6	3.7	6.8	2.9	4.8	5.1
10	3.8	4.8	4.7	3.6	5.3	3.8	30	3.4	2.3	6.1	7.4	1.4	4.8
11	2.0	2.4	2.9	4.4	3.8	1.2	31	8.1	6.6			5.8	3.6
12	4.7	4.7	4.9	4.1	4.0	6.7	32	4.6	2.5			2.8	2.6
13	3.1	5.5	4.2	3.8	2.2	2.8	33	1.6	2.4			4.4	2.5
14	2.5	5.3	6.0	4.0	2.0	6.0	34	5.1	5.6			8.8	4.2
15	4.3	7.0	4.7	2.7	1.8	2.7	35	4.4	3.1			6.6	5.0
16	2.7	3.4	2.7	3.7	1.0	3.4	36	5.4	5.1			7.4	7.4
17	4.0	3.3	4.7	2.6	1.1	5.0	37	10.1	4.4			2.8	4.4
18	4.5	5.9	3.2	4.0	1.9	4.1	38	4.0	4.0			7.7	5.0
19	2.9	4.3	2.7	3.4	2.4	4.6	39	4.9	4.2			5.5	7.2
20	5.1	2.7	3.5	2.6	3.0	3.1	40	4.4	2.8			4.4	3.9
Average								4.33	3.75	3.60	3.90	3.75	4.10
Standard deviation								±1.9	±1.5	±1.4	±1.0	±1.9	±1.5

Analysis of variance

SOURCE OF VARIATION	DEGREES FREEDOM	MEAN SQUARE	F RATIO	SIGNIFICANCE
A. Differences between subjects	39	7.8	5.2	high
B. Differences between fat levels.	2	1.2	0.8	none
C. Differences between fat types	1	0.1	0.7	none
D. Discrepance	177	1.5		
E. Reliability coefficient* $= \frac{7.8}{7.8 + 1.5} = 0.84.$				

St. error of differences between means $= \sqrt{1.5} \times \sqrt{\frac{1}{40} + \frac{1}{40}} = 0.2704.$

Difference between means necessary for significance $= 0.2704 \times 2.658\dagger = 0.71$ grams.

* Intraclass correlation coefficient is used as measure or reliability.

† 0 01 value of t.

ences permit a satisfactorily high reliability coefficient of 0.84, which means that had either the level or type (or both) of dietary fat altered fecal fat excretion, the findings would not have been "masked" by a wide and inconsistent range in

fecal fat excretion in given individuals, or by experimental error. The analysis further shows that there were no significant differences in total fat excretion due to the level or type of dietary fat.

Free fatty acid excretion. The average molecular weight of fatty acids of human fat is given as 277.2 by Hawk and Bergeim (15). This figure was multiplied by the milliequivalents of free fatty acids obtained by titration to estimate the weight of fecal free fatty acids. The free fatty acid content of lard was 0.38 per cent, and of HVO was 0.13 per cent (Table II). The summarized

TABLE V

Summary of free fatty acid excretion

GRAMS HVO OR LARD INCLUDED IN DAILY DIET	MEAN* FECAL FREE FATTY ACIDS PER DAY	
	HVO (.13% FFA)	Lard (.38% FFA)
	grams	*grams*
60	2.32	1.95
120	1.86	1.82
150	0.83	2.14

Analysis of variance

SOURCE OF VARIATION	DEGREES FREEDOM	MEAN SQUARE	F RATIO	SIGNIFICANCE
A. Differences between subjects	9	1.69	2.97	high
B. Differences between fat levels	2	2.14	3.76	high
C. Differences between fat types	1	1.35	2.37	slight
D. Discrepance	47	0.57		

Reliability coefficient $= \frac{1.69}{1.69 + 0.57} = 0.75.$

St. error of differences between means $= \sqrt{.57} \times \sqrt{\frac{1}{10} + \frac{1}{10}} = 0.108.$

* Difference in means necessary for significance $= 0.108 \times 2.878\dagger = 0.30$ grams.

† .01 value of t.

results from ten subjects receiving various amounts of lard and HVO as part of their daily diet are given in Table V.

These results indicate that fecal free fatty acids were not significantly altered when various amounts of lard were fed, while fecal free fatty acids decreased as the dietary content of HVO was increased. This means that fecal free fatty acid excretion was altered by the type and amount of dietary fat. The accompanying analysis (Table V), shows that significant differences between subjects were present, so that the reliability coefficient was 0.75, which is good reliability. Individual results are omitted.

TABLE VI

Summary of fecal fat iodine number determinations

GRAMS HVO OR LARD INCLUDED IN DAILY DIET	MEAN* IODINE NUMBER OF FECAL FAT	
	HVO (I#73)	Lard (I#65)
60	30.8	33.1
150	35.1	25.4

Analysis of variance

SOURCE OF VARIATION	DEGREES FREEDOM	MEAN SQUARE	F RATIO	SIGNIFICANCE
A. Differences between subjects	9	122.5	6.0	high
B. Differences between fat levels	1	28.7	1.4	none
C. Differences between fat types	1	136.5	6.7	high
D. Discrepance	28	20.3		

$$\text{Reliability coefficient} = \frac{122.5}{122.5 + 20.3} = 0.86.$$

$$\text{St. error of difference between means} = \sqrt{20.3} \times \sqrt{\frac{1}{10} + \frac{1}{10}} = 0.64.$$

* Difference in means necessary for significance = $0.64 \times 2.878\dagger = 1.84$.

† .01 value of t.

TABLE VII

Summary of fecal nitrogen excretion in 20 subjects

GRAMS LARD OR HVO INCLUDED IN DAILY DIET	MEAN* DAILY FECAL NITROGEN	
	HVO	Lard
	grams	*grams*
60	1.7	1.8
120	1.5	1.3
150	1.5	1.6

* Difference in means necessary for significance (.01 probability) = 0.37 grams.

TABLE VIII

Symptoms reported by 40 subjects while on 3000 calory diets containing various amounts of HVO and lard

	60 GRAMS FAT		120 GRAMS FAT		150 GRAMS FAT	
	HVO	Lard	HVO	Lard	HVO	Lard
Nausea	0	0	2	1	3	2
Vomiting	0	0	0	0	0	0
Persistent abdominal "fullness"	3	3	4	4	3	4
Epigastric pain	0	0	1	0	1	2
Diarrhea	2	2	2	1	1	3

Iodine number of fecal fat. The summarized results of the iodine number determinations on ten subjects following two levels of dietary lard and HVO are given in Table VI, together with an analysis of individual data.

It is evident that the iodine number of fecal fat was significantly altered by the type and amount of dietary fat. There were significant differences in iodine number between subjects, and the reliability coefficient was 0.86.

Fecal nitrogen excretion. The mean daily nitrogen excretion of 20 subjects on diets containing various amounts of HVO or lard are summarized in Table VII.

There was no significant alteration in mean nitrogen excretion attributable to the type or amount of fat in the diet. These values for fecal nitrogen are in agreement with those of previous investigators. Individual results are omitted.

Subjective symptoms. Subjects were questioned once each week. The symptoms reported by forty subjects while remaining on diets containing 60, 120, and 150 grams of added lard or hydrogenated vegetable oil daily are shown in Table VIII. The incidence of symptoms is so low that it is not possible to demonstrate statistically significant differences attributable to the type or amount of fat in the diet.

DISCUSSION

This study has shown that when fecal fat analyses are done on normal subjects having dietary fat intakes within the ordinary limits of daily fat consumption, greater differences in the quantity of fecal fat excretion can be expected due to individual variations in fat excretion than due to the level or type of edible fat in the diet.

Since the repeated tests, Table IV, do not differ significantly, the average daily fecal fat excretion for 40 subjects, based on *20 or 30-day fecal samples*, may be calculated as 3.91 grams, with a standard deviation of ± 1.01 grams. This means that 95 per cent of individuals, if 20- or 30-day fecal samples are analyzed, may be expected to have average daily fecal fat excretion of from 1.89 to 5.93 grams.

Daily fecal fat excretion based on *5-day fecal analyses* was found to be 3.91 grams with a standard deviation of ± 1.56 grams. (This was obtained by pooling the variance for the five-day tests.) This means that when only 5-day tests are made, 95 per cent of normal persons may be expected to have an average daily total fecal fat excretion of from 0.79 grams to 7.03 grams. Most reported values for fecal fat excretion, when the caloric intake is about 3000 per day, are within this range. Wollaeger (14), however, found daily fecal fat excretion to average 8.3 grams for three-day tests with subjects on a very high fat diet (208 grams of fat daily). In his study gastrointestinal tolerance to fat may have

been exceeded; it may be that the threshold for fat tolerance lies between 150 and 200 grams per day for sedentary human subjects.

The difference in standard deviation between 5-day tests, ± 1.56 grams, and 20- to 30-day tests, ± 1.01 grams, demonstrates a marked decrease in reliability of fecal analyses when only 5-day tests are made. The inaccuracy of tests of shorter duration thus becomes apparent.

Fat-balance studies have seldom tested fats at more than one level of dietary intake. The findings of this investigation emphasize a fallacy of the fat-balance method of study; since fecal fat excretion remains a constant value under ordinary dietary conditions, the "digestibility" of a food fat must depend entirely upon fat intake, and show an apparent improvement as more fat is included in the diet. Thus, in this study, the digestibility coefficient, as commonly expressed, of lard and hydrogenated vegetable oil was $\frac{93 - 4.13}{93} \times 100$ or 95.5 per cent at the lowest level of intake, and $\frac{168 - 4.19}{168} \times 100$, or 97.4 per cent at the highest level of intake. It has been suggested that a correction factor for metabolic fat be subtracted from the amount of fecal fat to determine the digestibility coefficient (7). This assumes that a constant amount of fecal fat is of endogenous origin, and is represented by the fecal fat excreted on a low fat diet. Use of such a factor does not make constant the digestibility of a fat when taken at different levels. If a metabolic fat factor of 2.1 grams (7) were used in this study, the digestibility coefficient at 168 grams intake would remain higher than at 93 grams (98.7 per cent and 97.5 per cent, respectively).

"Digestibility" studies have generally been conducted by feeding 50 to 100 grams of fat. From the foregoing considerations it becomes clear why the digestibility coefficient of countless low melting point, edible fats has been given as from $\frac{50 - 4}{50} \times 100$, or 92 per cent, to $\frac{100 - 4}{100} \times 100$, or 96 per cent.

The results of this study, together with the animal experiments reported by Hill, Sperry, and Bloor (18, 19), indicate the fat-balance studies in normal subjects are invalid as a method of measuring fat "digestion," since within ordinary limits of edible fat intake, fecal fat excretion is independent of the amount of dietary fat.

The values for fecal free fatty acids reported in the literature are all within the range of values found in this study, though no previous consideration has been given the free fatty acid content of the dietary fat. The fecal free fatty acids differ in quantity from those of the food fat; this indicates that fecal fat is not a residue of dietary fat. The interpretation of the changes in fecal free fatty acid excretion associated with changes in the type and amount of dietary fat cannot be given from the present study.

As with fecal fatty acids the iodine number of fecal fat tends to remain constant and different from the iodine number of dietary fat. This is in agreement with previous investigators (9, 20). The saturation of dietary fat, however, appears capable of influencing that of fecal fat. More knowledge of fat metabolism will be required to explain this effect of dietary fat on fecal fat.

Contrary to the study of Smith (21) in which 80 subjects ate unknown and uncontrolled amounts of food and fat, in this study no significant differences in symptoms occurred due to the type or amount of dietary fat. That so few symptoms were reported is probably because the subjects had a constant daily caloric intake for six weeks with no opportunity for dietary indiscretion.

SUMMARY AND CONCLUSIONS

1. Normal subjects were given mixed, 3000 calorie daily diets containing 93, 140, and 168 grams total fat, of which 60, 120 and 150 grams, respectively, were lard or hydrogenated vegetable oil (Crisco). Each level of each type of fat was given for one week. Stool collections were made the last five days of each week.

2. Neither the level nor the type of dietary fat used in these experiments produced significant changes in total fecal fat excretion in 40 subjects. This indicates that fat-balance, "digestibility" studies are of questionable validity, since within ordinary dietary limits fecal fat excretion is independent of dietary fat intake when lard and the hydrogenated vegetable oil (Crisco) are used.

3. The free fatty acid content and iodine number of fecal fat differed from those of the dietary fat in ten subjects, indicating that the former is not an "undigested" residue of the latter.

4. Dietary fats of varying composition and given in different amounts alter the free fatty acid content and iodine number of fecal fat. The interpretation of these findings is not apparent.

5. Twenty subjects showed insignificant changes in fecal nitrogen excretion attributable to the type or amount of dietary fat.

6. Forty subjects showed no significant differences in subjective symptoms reported while consuming various dietary levels of lard or hydrogenated vegetable oil (Crisco).

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THE ASSAY OF CHOLECYSTOKININ AND THE INFLUENCE OF VAGOTOMY ON THE GALL BLADDER RESPONSE

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INTRODUCTION

Certain studies reported in the literature have suggested that the effectiveness of various gastrointestinal hormones and chalones depends on the anatomic and functional integrity of the nerve supply to the organ under investigation. As early as 1903 Fleig found that the secretory effect of a soap extract of the intestinal mucosa was abolished by atropine. Thomas and Crider (1944) found that vagotomy reduced by approximately 50 per cent the volume of pancreatic juice secreted by the unanesthetized dog following instillation of acid into the intestine. The enzyme concentration, as measured by the specific gravity and nitrogen content of the secretion, was also reduced in some of the experiments. Administration of atropine or hyoscyamine also reduced the volume and nitrogen content of the pancreatic juice secreted in response to secretin (Thomas and Crider, 1946). Recently Harris et al. (1947) reported that while enterogastrone preparations inhibited distension-induced motility of the vagally innervated stomach, in the vagally denervated stomach "enterogastrone" was either without effect or actually augmented the gastric motility. These authors found also that fat in the intestine inhibited the gastric motility in both the vagally innervated and denervated stomach.

It has been shown in this laboratory (Snape, 1947) that while the gall-bladder evacuation in response to fat in the intestine was not abolished by vagotomy, there was nevertheless a distinct delay in the response. One of several possible explanations considered was that vagotomy reduced the sensitivity of the gall-bladder to the cholecystokinin formed in the intestine in the presence of fat. While experiments on dogs with transplanted gall-bladder (Houssay and Rubio, 1932) and isolated atropinized strips of the guinea pig's gall-bladder (Doubilet and Ivy, 1938) showed that the denervated organ will respond to cholecystokinin, no information is on hand showing whether the denervated organ acts similarly to the intact organ in situ.

The present study was undertaken to obtain this information by determining the effects of cholecystokinin on the evacuation of the gall-bladder in situ in unanesthetized dogs both before and after supradiaphragmatic vagotomy.

METHODS

In order to test whether denervation affected the response to a standard dose of cholecystokinin it was found necessary to assay the hormone. The assay

procedure, not having been hitherto described, is also presented at this time. The procedure used has the advantages of not interrupting either the blood supply or the innervation of the organ and the avoidance of anesthesia. In addition the procedure permits the repeated use of the same animal. Two of the four dogs employed in the present study have been used in this and similar studies for more than three years and the other two for nearly 28 months.

The animals used were healthy dogs thoroughly conditioned to laboratory surroundings. They were equipped with permanent fistulas of the stomach and duodenum fitted with metal tubes by the method previously described (Thomas, 1940). The duodenal fistula was established opposite the papilla of the common bile duct (Snape and Thomas, 1945). Bile was collected by passing a specially designed glass cannula into the common bile duct by way of the duodenal fistula, as suggested by Scott and his co-workers (1941) for temporary intubation of the pancreatic duct. The glass bile cannula was kept in place by the action of the sphincter of Oddi. The stomach was drained through the open gastric fistula, thus insuring against emptying of the gall-bladder by the presence of acid gastric juice in the intestine.

The influence of vagotomy was studied by determining whether following severance of the vagus nerves any change occurred in either the threshold dose of cholecystokinin or in the latent period of the response. A total of 15 separate fractions of hog intestinal mucosa were used to first determine whether the minimal dose of a given extract varied in the different animals and whether animals were on some occasions more responsive than on others. The minimal effective dose, as determined by our procedure, was found to be satisfactorily constant and is now being used in this laboratory as a unit of potency.

The procedure was as follows. A meal of 650 grams of ground lean raw beef was fed each dog about 21 hours before the test. After cannulating the bile duct through the opened duodenal fistula the biliary cannula was connected with a recording tambour by means of rigid pressure-resistant rubber tubing. A glass side arm was introduced in the rubber tubing for the purpose of removing bile and regulating pressure within the system. Kymographic tracings were made and in this manner the muscular activity of the gall-bladder could be recorded when approximately as little as 0.2 cc of bile was expelled by the bladder.

The extracts being tested for cholecystokinin activity were prepared by several different procedures. (Friedman and Snape, 1948, to be published). A weighed amount of extract was dissolved in physiological saline solution and administered intravenously. The volume of fluid injected was 2 to 4 cc. Provided the gall-bladder was not already empty, certain extracts of duodenal mucosa when given in adequate doses always caused a motor response of the gall-bladder while other intestinal extracts were found to be without effect. By gradually decreasing or increasing the dose of extract being injected intra-

venously a minimal effective dose was eventually attained. An interval of at least twenty minutes between consecutive injections was allowed in order to avoid accumulative effects.

When persistent negative effects were obtained after several injections of the same extract in increasing doses, about 25 cc of 20 per cent cream was administered by duodenal tube, to check for fullness and responsiveness of the gall-bladder. An absence of bile flow in response to the fat was taken to indicate that the gall-bladder was either empty or non-responsive; a flow of bile

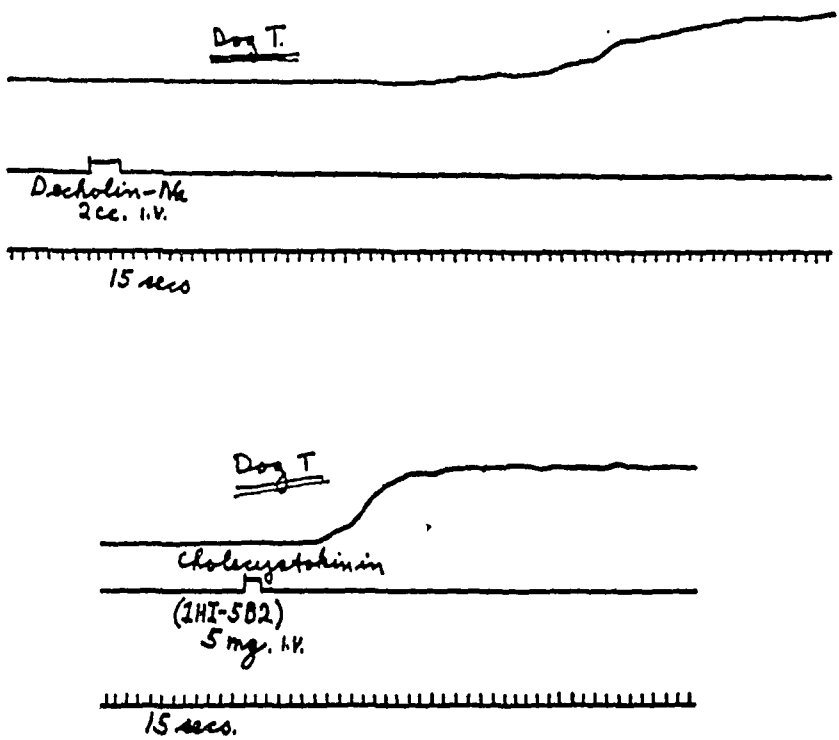

FIG. 1a. (lower record). Prompt response to administration of 5 mg. of intestinal mucosa extract. This dose was determined to be 2.5 times the minimal effective dose. 1b. (upper record). The delayed response to the administration of 40 mg. of the sodium salt of dehydrocholic acid (20 cc. "Decholin-Na") illustrates the effect of the flow of liver bile.

within ten minutes of the fat instillation was taken as evidence that the extract, to which there had been no response, was void of cholagogic action in the dosage used. Other possible causes of negative results were given due consideration.

The development of refractoriness to tissue extracts is a possibility that must always be borne in mind. However, to date we have had no evidence for such a condition. One animal has, during a period of four months, received about 20 injections of the same intestinal mucosa extract without developing a refractory state. Blockage of the bile cannula is evidenced by leakage of bile around the cannula rather than a flow through it.

False positive results could, conceivably, occur due to choleretic substances, such as secretin (Agren, 1934; Tanturi, Ivy, and Greengard, 1937) or hepatocrinin (Friedman and Snape, 1945) which are present in intestinal extracts and which increase the output of bile from the liver independent of any action on the gall-bladder. However, the increase in biliary duct pressure so produced is easily distinguished from that due to contraction of the gall-bladder. Choleretic substances such as certain intestinal extracts or bile salts, do not cause an immediate increase in biliary duct pressure; with our method of recording there is seen to be only a gradual increase in pressure after a considerable delay (Fig. 1b). On the other hand, substances acting on the gall-bladder produce an abrupt increase in pressure after a short latent period (Fig. 1a).

Evacuation of the gall-bladder apparently in response to the association of pricking the skin with a hypodermic needle was observed on several occasions in only one of our dogs. Such a condition, of course, interferes with the assay procedure and may be detected readily by the intravenous introduction of a placebo such as saline.

RESULTS

The sphincter of Oddi is kept patent throughout the experiment by the presence in the bile duct of the glass cannula. This prevents the state of tonus of either the sphincter or the duodenal musculature from becoming a factor in determining or modifying the results. We found that a given extract of tissue when administered to several animals gave comparable results (Table I). The cholagogic response observed was characteristic of each animal and could be duplicated rather closely with the same dose of extract.

In Table II are given representative results of several assays. We tentatively define a unit of cholecystokinin as the minimal amount which when administered to the unanesthetized dog (15 to 20 kilograms body weight) under the above conditions will exert a detectable motor effect on the gall-bladder in a majority of the animals tested. Further study of the various factors involved is required before the proposed unit can be defined more strictly. In our hands the method has proved a valuable means both for detecting the presence of cholagogic substance in extracts and for rapid assay for potency.

By the method described above we observed that the latent period for expulsion of bile following injection of an effective dose of cholecystokinin (with one exception) ranged from 50 to 68 seconds, the average on three dogs being 61 seconds, before vagotomy. This compares favorably with the results of Royer and Manfredi (1944) who used the unanesthetized dog with temporary exposure of the bile duct papilla. Except possibly with minimal doses, the latent period was not affected by the amount of cholecystokinin injected. The duration of contraction of the gall-bladder was roughly in proportion to the amount

of cholecystokinin. Observed deviations from this rule were possibly due to variations in the extent of previous filling of the gall-bladder.

TABLE I

	DOSE ADMINISTERED PER DOG				
	1 mg.	2 mg.	3 mg.	4 mg.	5 mg.
Extract no. 2HI-6B2					
Dog T	−	−	+		+
Dog M	−	−	+	+	+
Dog C	−	−	+		+
Extract no. W3HI-2B(Q3)5B					
Dog T	+	+		+	
Dog M	+	+		+	
Dog C	−	+		+	
Dog B	−	+		+	

Gall bladder motor response obtained on intravenous administration of various doses of intestinal mucosa extracts.

TABLE II

INTESTINAL EXTRACT NO.	NO. OF ASSAYS	NO. OF DOGS	MINIMAL EFFECTIVE DOSE MG. (= 1 UNIT)	REMARKS
1HI-5B2	9	3	2	
3HI-2BQ26B	7	3	10	Dogs vomited on 2 mg. doses
2HI-6B2	13	3	3	
4HI-W4	8	3	3	
3HI-2BQ63B	9	4	10	Gastric secretion and intestinal motor activity on 4 mg. doses
W3HI-26Q35B	12	4	1.5	

Minimal effective dose (i.e., mg. per unit) of various intestinal mucosa extracts as determined by the response of the vagally intact gall bladder.

TABLE III

	NO. DOGS	NO. ASSAYS	MINIMAL EFFECTIVE DOSE	LATENT PERIOD, SECS.		
				Shortest	Longest	Average
			mg.			
Before vagotomy	3	9	2	50	68	61
After vagotomy	3	12	2	34	95	69

Response of the gall bladder to "cholectystokinin" (Extract No. 1 HI-5B2) administered before and after supradiaphragmatic vagotomy.

When the latent period and the effective minimal dose had been determined as described above supradiaphragmatic vagotomy was performed under aseptic conditions. Two weeks postoperative the experiments were repeated using

the same preparations of intestinal extracts. Each of the animals had complete vagotomy judging by the negative response of the gastric glands following intravenous insulin.

The minimal effective dose of cholecystokinin was not changed by vagotomy in any of the animals (Table III). The latent period was increased in only two of twelve experiments. The average latent period in the twelve experiments was 69 seconds (control, 61 seconds) and ranged from 34 to 95 seconds.

DISCUSSION

These experiments show that the response of the gall-bladder to cholecystokinin given intravensouly is not significantly affected by vagotomy. Thus they show that the changes (reported elsewhere) in the response of the gall-bladder to fat and other substances in the intestine after vagotomy were due to causes other than changes in the responsiveness of the gall-bladder to the circulating hormone. The following possibilities remain: Vagotomy may (1) interrup reflex paths normally involved in gall-bladder evacuation, (2) delay or decrease the output of hormone from the intestine, or (3) so modify intestinal function as to reduce the effectiveness of intestinal stimuli.

SUMMARY

1. A method is described for testing the cholagogic action of intestinal mucosal extracts on the gall-bladder in situ in the unanesthetized dog.

2. A dog unit of cholecystokinin is defined.

3. Neither the latent period nor the minimal effective dose of cholecystokinin are influenced by vagotomy.

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AN EXPERIMENTAL STUDY OF GASTRIC EMPTYING IN THE VAGOTOMIZED DOG[1]

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In an experimental study in 1939 we described the effect of thyroid medication on gastrointestinal motility. It was noted that thyroid stimulates gastrointestinal motility to a marked degree in the normal dog. It was also observed that thyroid stimulates motility in bilateral subdiaphragmatic vagotomized dogs. Of particular interest in another experiment was the inhibiting effect of atropine upon the accelerating effect of thyroid therapy. The atropine counteracted the effect of thyroid. These experiments further confirmed Kendall's work on thyroxine. He found that after the vagus nerves had been paralyzed with atropine their sensitiveness to stimulation could be restored with iodothyrin. Kendall concluded that thyroid affected the tonus of the vagus nerve. The exact mechanism, by which thyroid acts is not definitely established. However, since thyroid is a cellular stimulant, it is probable that its mechanism of action is by way of stimulation of gastrointestinal cellular elements.

Thyroid action depends upon the integrity of the autonomic nervous system. The action of thyroid is believed to stimulate gastric emptying in three ways. (1) effect on the nerve endings, (2) acts on the myoneural junctions, and (3) an effector cell stimulation.

We have further confirmed the effect of thyroid on gastrointestinal motility in the present experimental study.

ETAMON

It was of interest to note what stimulating effect, if any, thyroid medication had upon gastrointestinal motility following the intramuscular injection of $2\frac{1}{2}$ cc. of a 10% solution of Etamon, (tetraethylammonium chloride). Accordingly, Etamon was given to two normal dogs. In these animals the roentgen examination made five hours after a barium meal, showed a dilatation with a large gastric retention. In another study of three bilateral vagotomized dogs in which 1 cc. containing 1 mg. of thyroxine was given for six days prior to the injection of Etamon a large gastric retention was revealed in two of the three dogs. Thyroxine did not appear to produce a stimulating effect on gastric motility following the administration of Etamon.

Since thyroid medication is not effective when Etamon is given, this is

[1] The expense of carrying out these experiments was defrayed in part by the Dr. Julius Friedenwald Fund. Etamon was supplied through the courtesy of Parke Davis & Co.

probably due to the fact that Etamon completely paralyzes both the sympathetic and parasympathetic nervous systems.

PROSTIGMIN

The effect of prostigmin on the bilateral vagotomized dog was variable. In seven dogs, 0.5 mg. of 1–2000 solution was injected subcutaneously in two doses, one given immediately following the administration of barium, the other one hour later. Roentgen studies made six hours after the barium meal revealed complete emptying of the stomach in three dogs, a small gastric retention in one and in three the stomach was markedly dilated, with a large retention.

MECHOLYL

Mecholyl was used to determine its effectiveness on emptying the stomach following bilateral vagotomy. Five dogs were given 1 cc. (25 mg.) of Mecholyl chloride subcutaneously. In one dog there was complete emptying, while four dogs revealed a large gastric retention.

ACETYLCHOLINE CHLORIDE

The effect of acetylcholine on gastric emptying in the vagotomized dog was determined in five dogs. Two doses were given subcutaneously, 1 cc. (25 mg.) immediately after the administration of the barium meal and the other one hour later. In 1 dog the stomach was completely empty, 1 showed a trace of barium, 1 a slight retention and in 2 there was a moderate gastric retention in five hours. Acetylcholine seemed to be highly effective in augmenting gastric emptying.

DORYL (CARBAMYLCHOLINE CHLORIDE)

Five dogs were used to determine the effect of Doryl, on gastric emptying following bilateral vagotomy. 1 cc. (25 mg.) of Doryl was injected subcutaneeously in two doses following a barium meal.

In 1 dog the stomach was completely empty, in 1 a trace of barium was retained, in 1 a very small retention and in 2 a moderate gastric retention was noted six hours after a barium meal. The effectiveness of Doryl is similar to that of acetylcholine.

SUMMARY

Prostigmin, mecholyl, acetylcholine and Doryl are parasympathomimetic drugs which stimulate gastric motility. It seems that acetylcholine and Doryl are more effective than prostigmin and mecholyl in emptying the stomach of the bilateral vagotomized dog.

Thyroid stimulates gastric emptying in the vagotomized dog. The effect of thyroid is similar to that observed following the use of acetylcholine and Doryl. Thyroxine did not produce satisfactory gastric emptying in the normal and vagotomized dogs following the use of Etamon.

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PHARMACOLOGICAL ASPECTS OF GASTRIC SECRETION[1, 2]

PART I. THE EFFECT OF OPIUM ALKALOIDS AND AN "ALLIED" DRUG DEMEROL ON POUCH SECRETIONS IN DOGS

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INTRODUCTION

In the relief of pain in the ulcer patient, the use of opium alkaloids and more recently, demerol, has been standard practice. Morphine is seldom necessary in the care of the ordinary patient. However, it must be resorted to in instances of perforation or severe pain associated with a bleeding ulcer. The capacity of these drugs to allay pain and reduce mental tension has been well documented, but inspection of the literature reveals confusion relative to their effect on gastric secretion.

In casting about the laboratory for a "round-the-clock" depressant, it was felt that a concomitant study of the effect on gastric secretion of these various "standard" drugs utilized as adjuncts in ulcer therapy merited investigation. Certainly, in the literature the effect of these drugs upon gastric secretion is not clearly defined. This study appeared necessary before one could safely assume that the employment of such drugs aided the healing more than they abetted the diathesis.

REVIEW OF THE LITERATURE

Opium alkaloids and an allied drug, Demerol. Opium contains two chemically distinct groups of alkaloids. The phenanthrene group, represented by morphine and the esters formed by replacing the H of one or both hydroxyls of morphine, is the more important. The second group, or isoquinone derivatives, represented by papaverine is of lesser importance. In general, the action of these two groups differs, dependent upon their chemical structure (15, 57).

Our attention has been focused upon the phenanthrene derivatives, because of the frequency with which these drugs are used for the relief of pain. Although a great interest has been manifested in the analgesic effect of these drugs, a small number of investigators have studied their effect on gastric motility still fewer their effect on gastric secretion. Only isolated papers have

[1] This research represents an abridgement of a thesis submitted to the Graduate School of the University of Minnesota in partial fulfillment for the degree of Doctor of Philosophy in Surgery.

[2] This work was supported by the following grants: The Augustus L. Searle Fund for Experimental Surgical Research, the Dr. and Mrs. Harry B. Zimmerman, the Dr. Burneice Moriarty, and the Robert A. Cooper Funds for Surgical Research.

appeared concerning the individual effects of the other derivatives on gastric function.

Hitzig (20) in 1892 first aroused interest in the effect of morphine on gastric secretion in man. He believed that morphine addicts secreted the drug into the stomach and that this inhibited the secretion of hydrochloric acid. Further, that incidental to the withdrawal of this drug an increased secretion of hydrochloric acid took place. Kim (27, 28) stated that the level of acid was lower in morphine addicts than in normal individuals. Upon withdrawal of the drug, the gastric secretion of acid gradually returned to normal. He stated, however, that in addicts when morphine was given, the acid and volume increased.

In the same year, Leubuscher and Shaeffer (33) studied, in normal individuals, the effect of morphine on gastric secretion by the intubation methods. With small doses (morphine 0.02 to 0.03 grams; opium 0.15 grams) by mouth, there was a reduction and delay of hydrochloric acid secretion. The subcutaneous administration produced a marked reduction of the hydrochloric acid secreted. Others have confirmed this finding with morphine (22, 62, 29) and with tincture of opium (1) given by various routes.

Alwens and Rauth (3) observed in man a marked gastric secretion after opium alkaloid administration. Jarno and Marko (24) confirmed this finding in patients with anacidity.

In experimental animals, however, the results are somewhat different. Kleine (30) 1897, in dogs with stomach fistulas, observed a strong stimulating influence of morphine with 0.01 to 0.04 grams subcutaneously. Riegel (52), Hirsch (19), Bickel and Pincussohn (aqueous opium) (7), Smirnow and Schirokij (56), and Efet (13) have noted a similar effect in dogs with various types of gastric fistulas. Wang, Probaska and Palmer (62) noted inconsistent results in pouch dogs with morphine administration in similar dosages.

In pigs with gastric fistulas, 0.6 grams of morphine produced a reduction in gastric acidity. Furthermore, smaller doses (0.02 grams) gave similar results (38).

Magnus (34) 1908 performed an extensive work on cats, dogs, and rabbits. X-ray studies were made periodically after the ingestion of a barium meal. He noted after the injection of morphine a severe contraction of the "antral sphincter" and pylorus with a marked retardation of the emptying time of the stomach. Sato (54) confirmed this work in rabbits. Plant and Miller (50) by means of the balloon technique and, in addition, fluoroscopic examination in dogs and cats observed a sudden decrease in tone and a diminution in the amplitude and frequency of the large contractions of the stomach with morphine administration. Mixed alkaloids of opium (as pantopon, codeine, papaverine, narcotine and heroin) all produced the same results as did morphine. Others have observed a prolongation of the emptying time of the stomach in dogs with

morphine (55, 19) and tincture of opium (11). Cohnheim and Modrowski (11) observed an accelerated emptying time of the stomach in dogs with morphine sulphate 0.01 grams.

In man, Von den Velden (61) confirmed the work of Magnus with morphine utilizing the same technique. He described a picture not unlike an hour-glass stomach. Other investigators have noted only a retardation of gastric motility with morphine (4), opium alkaloid (3) and pantopon (53). Pancoast and Hopkins (43) also used the x-ray technique in man. Morphine, 10-15 milligrams, was injected subcutaneously. These observers found the retardation of gastric motility to be characteristic and the hour-glass stomach alluded to by Von den Velden to be a rarity.

The literature appears to be devoid of any investigations with special reference to the effect of codeine, dilaudid and paregoric on gastric secretion.

Demerol was synthesized by Eisleb and Schaumann (14) in 1939. These authors showed that this drug combined the antispasmodic effects of atropine and papaverin with the analgesic properties of morphine. Such characteristics theoretically would appear to be ideal in ulcer therapy.

Gruber, Hart and Gruber (16) in 1941 reported an extensive work with demerol. Unanesthetized dogs were given demerol in doses from 0.5 to 2.0 milligram per kilogram of body weight by slow intravenous injection. These authors concluded that this drug had no spasmolytic action on the stomach or pylorus in the unanesthetized dog.

Climenko (8) 1943 stated that demerol is a potent spasmolytic agent. The action is in part due to depression of the parasympathetic endings but is primarily the result of a direct papaverine-like depression of the muscle fiber. This effect has been observed under experimental conditions on isolated smooth muscle, and in man under clinical conditions.

Batterman and Himmelsbach (6) in summarizing the literature on the effect of demerol on the gastro-intestinal tract in animals stated that the results had been variable depending upon whether the segment was isolated or in situ, the species of animal used, and the method of study. Batterman (5) by intubation studies with balloons of various portions of the gastro-intestinal tract, including the stomach, revealed an antispasmodic response with fifty to one hundred milligrams of demerol administered intravenously in 84% of twenty-seven humans tested.

Hoffman (21) stated that demerol delayed the emptying time of the stomach by twenty per cent. Both, Hecht and Yonkman (42) studied a group of nine patients with benign duodenal or gastric ulcers. The results were uniformly good with demerol in relieving pain even when the ulcer was penetrating in type and accompanied by severe distress with radiation to the back or over the anterior thoracic wall.

The majority of evidence suggests, therefore, that demerol in man has a spasmolytic effect on the gastro-intestinal tract. However, no work has appeared so far concerning any effect of this drug on gastric secretion either in the experimental animal or in man.

METHODS OF STUDY

Experiments on dogs with isolated gastric pouches. This study was carried out upon standardized Heidenhain and Pavlov pouch dogs. The "isolated" gastric pouch was fashioned in the classical manner. The fifteen pouch dogs used, maintained a good general state of nutrition, were free of infection and secreted clear pouch juice.

Method of standardization in the fasting state. A 16-hour fasting period preceded each experiment. Pouch secretions were collected under similar conditions beginning at 9:00 A.M. for five consecutive hours on three separate occasions. Each hourly sample was collected in an individual test tube. At the conclusion of the 5-hour period, each sample was titrated with one-tenth normal sodium hydroxide using "Topfer's" reagent and phenolphthalein as indicators for free and total acid. Volumes were measured to one-tenth cubic centimeter.

An average was computed on the basis of the three separate tests for each hour for all factors (free, total acid and volume). In this manner, a mean standard fasting curve was established for each animal.

All dogs were given one or more days' rest between experiments. The diet consisted of table scraps supplemented by dog biscuits. Regular feeding schedules were maintained during resting days.

Procedure for testing substances on pouch dogs. In all subsequent experiments with pouch dogs, food pans were removed sixteen hours previous to the test period. Water was allowed up until, but not during, the test period. Pouch juice was collected under similar conditions for one hour from 9:00 A.M. to 10:00 A.M. (occasionally two one-hourly fasting specimens were collected). The substance to be tested then was given to the experimental animal. Subsequently, hourly samples were collected in clean test tubes. At the conclusion of each test, each hourly sample was measured and titrated for free and total acid by the method previously described.

Occasionally there was a marked variance in the fasting sample on the test dog as compared with the anticipated fasting level as observed on the standardization curve. The retention of food products in the animal's stomach from the previous day's feeding or the inadvertent failure to remove the food pan may be possible explanations.

RESULTS

Opium alkaloids and an "allied" drug, demerol

Morphine sulfate. The dosage of morphine sulfate administered was of the magnitude (in most instances) considered to be therapeutic for man. In these initial experiments, no attempt was made to correlate dosage with the body weight of the animal. Veterinary morphine was used in certain instances; in other experiments the morphine sulfate administered was obtained from the University Hospital Pharmacy. The effect produced was similar in all respects. The drug was dissolved in a few cubic centimeters of distilled water utilizing sterile precautions. The injection was made under the loose skin of the back.

Seven experiments were performed on six Heidenhain and Pavlov pouch dogs with morphine sulfate, 15 milligrams. In five of the seven experiments carried out a definite moderately strong to strong stimulation of free acid and volume was observed in the pouch secretions. Vomiting and defecation was a common observation which usually occurred shortly after the injection.

Subsequently, with the same technique, five experiments were carried out with morphine sulfate, 30 milligrams. A strong stimulation of free acid and volume was noted in four of the five tests. An equivocal mild stimulation was observed in the fifth experiment.

Dilaudid hydrochloride. Because of the intimate relationship of the opium alkaloids in chemical structure and analgesic action, one might anticipate that these drugs would exert a similar effect on pouch secretion. The correctness of this supposition is borne out in the subsequent experiments with dilaudid.

Twelve experiments were carried out in four Heidenhain and Pavlov pouch dogs. Each dog was tested on two separate occasions: On one occasion 1 milligram was injected, on the other 2 milligrams were used. The smaller dose of dilaudid produced no uniform response. Utilizing the larger dose, 2 milligrams, two of these four dogs showed a definite stimulation effect. This suggested that with the increase in dosage there was a trend towards stimulation of pouch acidity. The other point of interest is the difference of the fasting free acid values of these experimental animals on the two different occasions. This difference may be explained by an oversight to remove food pans the previous day, or by the presence in the stomach of undigested food ingested 16 or more hours earlier. Such divergent fasting levels makes one hesitant to speak of a definite stimulation or depression effect of any substance unless such results are fairly uniform. Otherwise it is preferable to speak in terms of a trend.

In the four remaining tests, 4 milligrams of dilaudid was injected subcutaneously. The strikingly uniform results obtained with the injection of 4 milli-

grams of dilaudid suggest that the dosage is the determining factor in the production of a stimulation effect. In these latter tests, it should be noted that the initial fasting free acid level approximated closely the standardization curves for these four dogs.

Paregoric. In the following experiments with paregoric, the similarity of the pouch secretory response to the opium alkaloids is again observed. These results parallel well the results noted with morphine and dilaudid. One is tempted to generalize that drugs bearing the same basic formula produce a similar secretory response. One must remember, however, that paregoric contains other drugs in addition to the opium alkaloids.

Three pouch dogs (two Heidenhain, one Pavlov) were tested with this drug. Twenty cubic centimeters of paregoric mixed with 50 cubic centimeters of distilled water were instilled into the stomach by tube. Distilled water alone has been observed to exert no effect on pouch secretion in experiments of short duration (44, 39). Because of the fairly close uniformity of these results with paregoric, it seems fair to state that with this dosage this drug stimulates moderately the pouch acidity and volume curve.

Codeine sulfate. The experiments with codeine exemplify well the exception to the rule. This is the only opium alkaloid tested which failed to produce a stimulation of pouch secretion. The doses were large and the experiments similarly planned as before. The reason for this deviation from the anticipated result is not clear

Eight experiments were performed on three pouch dogs. Here again it appeared advantageous to subject the same pouch dogs to different doses in order to better evaluate the response. The codeine sulfate was prepared in the usual fashion and injected hypodermically.

Four experiments were performed with 30 milligrams of codeine, three with 60 milligrams, one with 120 milligrams. In these experiments, there was no significant stimulation effect with the dosage used. With the exception of two tests (dog No. 11, 30 milligrams and dog No. 44, 60 milligrams) an almost perfect plateau "curve" was recorded. This observation also applied to the volumes of juice secreted. It is apparent that a depression effect cannot be excluded.

Demerol.[3] The combination of atropine- and morphine-like properties in one drug would appear to be promising for the ulcer patient. The value of atropine in ulcer therapy is accepted as is the analgesic effect of the opium alkaloids. Consequently, it was felt that the effect of demerol on pouch secretion merited investigation. No literature is available concerning a similar study.

Four pouch dogs were tested with demerol on eight separate occasions. Two

[3] Demerol for these experiments was kindly supplied by the Winthrop Chemical Company.

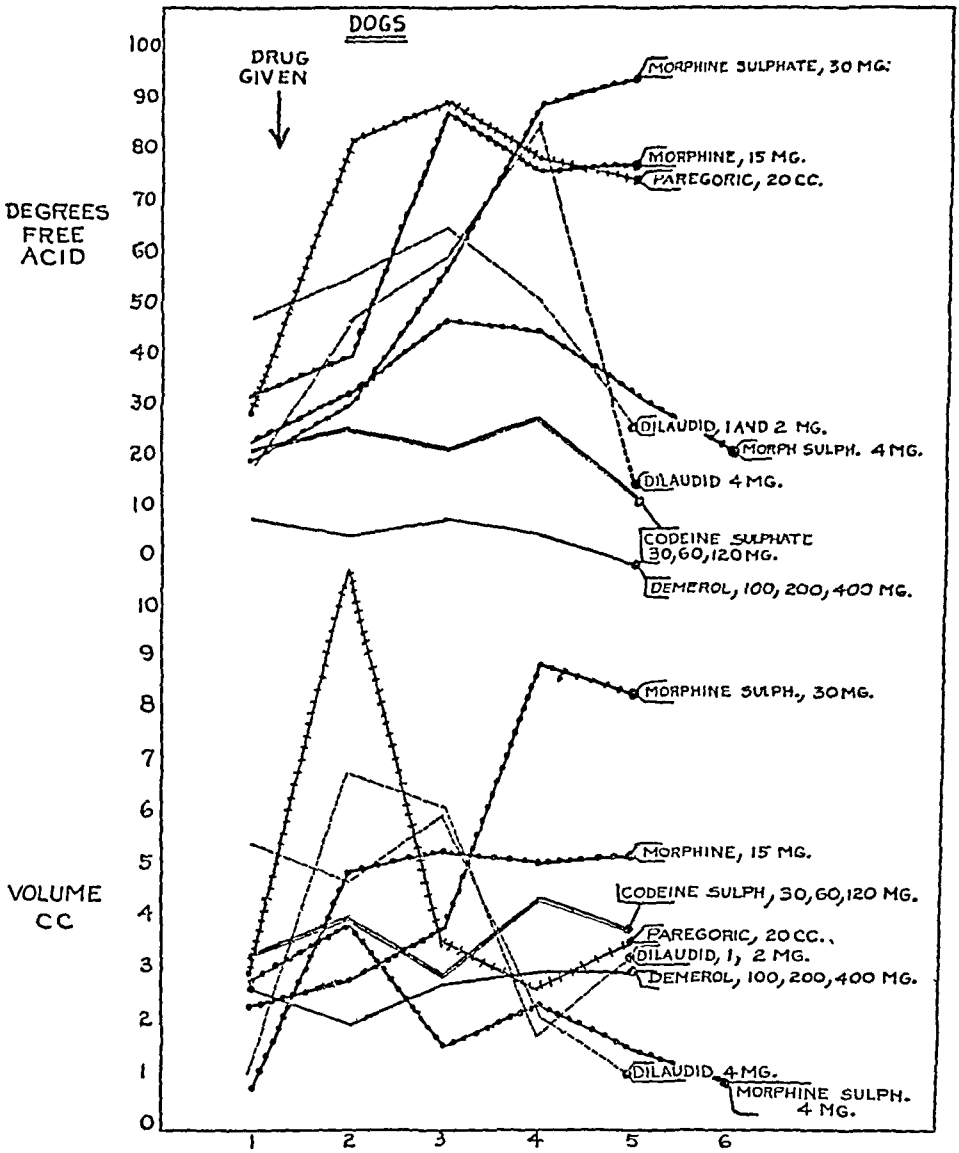

FIG. 1. These curves represent the average response of all dogs tested with the various dosages of the drugs listed. Certain pouch dogs failed to secrete any free acid during the test period. However, these dogs were known to be capable of secreting free acid, consequently, their responses were *included in the above computations.*

Paregoric, morphine sulfate, and dilaudid hydrochloride appeared to be moderately strong stimulators of free acid. The magnitude of the dosage conditioned somewhat the response. With smaller doses of dilaudid (1 to 2 milligrams) the acid response is equivocal. Also, with morphine sulfate (4 milligrams) the response is diminished but nevertheless definite. The free acid curve for both codeine and demerol are unaffected by the administration of the drug.

The volume responses in the main parallel well the free acid curve. Drugs which stimulate the free acid secretion likewise produce an increased volume. The volume curves following codeine and demerol administration continue unaffected. Equivocal volume responses are noted with the smaller dosages of dilaudid and morphine.

tests were carried out with 100 milligrams; three with 200 milligrams; and three additional tests with 400 milligrams. All injections were made intramuscularly (some were probably subcutaneously) after a one-hour sample of pouch juice

had been collected in the usual fashion. These doses are large. Particularly so if one considers the usual therapeutic dose in man and contemplates a comparison of the body weight of the human and dog. There were no ill effects noted in any dogs subjected to 400 milligrams of demerol subcutaneously.

The gastric secretory response in the dog, an animal one-third to one-fourth the average weight of an adult human, given at least four times the clinically considered therapeutic dose of demerol in man, does not vary from the fasting level obtained previous to administration of the drug. Some experiments do not exclude a depression effect. Also, the monotonous similarity of the volumes recorded after the fasting specimen further suggests the complete absence of any effect on the gastric secretory mechanism.

A composite graph of the average response of pouch dogs to the variously administered drugs has been made (Fig. 1).

SUMMARY

Morphine sulfate in dosage from 4 to 30 milligrams produces a moderate to marked stimulation of pouch acidity and volume.

Dilaudid hydrochloride in dosages varying from 2 to 4 milligrams causes a moderate to strong stimulation of pouch acidity and volume. Twenty cubic centimeters of paregoric produces a similar response.

No significant effect on pouch acidity and volume was noted with 30 to 120 milligrams of codeine sulfate nor 100 to 400 milligrams of demerol hydrochloride. There was a complete absence of toxic reaction with this dosage of demerol.

The stimulation or depression effect on pouch secretion was observed with all the drugs tested both in vagally denervated and vagally innervated gastric pouches.

(References will be found at the conclusion of part IV.)

PART II. THE PRODUCTION OF "PEPTIC" ULCER IN GUINEA PIGS AND CATS WITH MORPHINE SULPHATE ALONE AND COMBINED WITH FRACTURES

The importance of the acid factor in the genesis of "peptic" ulcer is now well appreciated. Because of the effect observed in the pouch secretions of dogs, a study was made with smaller experimental animals. In order to prolong the evanescent action of the drug, a mixture of morphine sulfate was prepared with beeswax after the method of Code and Varco (9). The holding of the drug with beeswax allows a slow and steady release of the active ingredient. The formula used initially in the studies on guinea pigs was as follows:

Morphine sulfate	1,000 milligrams
Beeswax	1 cubic centimeter
Mineral oil	4 cubic centimeters

1/100 c.c. = 2 mg. of morphine sulfate

Veterinary morphine was used. Veterinary morphine is a somewhat more impure mixture than that which is used in humans. Consequently, the actual morphine dosage is less than that which is indicated.

Experiments were carried out with this mixture of morphine sulfate in beeswax on pouch dogs. The stimulation effect on gastric secretion was observed. Therefore, we were assured of an active compound.

RESULTS

First, a series of six guinea pigs was used. Guinea pig No. 1 received 20 milligrams of morphine sulfate per kilogram of body weight. The dosage was doubled for each succeeding animal in this series in an attempt to determine

TABLE I

GUINEA PIG NUMBER*	WEIGHT	MORPHINE SULFATE	DAILY DOSAGE OF MORPHINE SULFATE	SURVIVAL	MACROSCOPIC RESULTS
	grams	*mg./kilo*	*mg.*	*days*	
1	424	20	9	44	One area of definite gastric erosion, numerous hemorrhagic areas
2	497	40	20	48	Numerous hemorrhagic areas over the gastric mucosa. Gastritis and duodenitis
3	421	80	34	11	3 gastric ulcers, 2 in continuity on the greater curvature
4	500	160	80	23	Negative
5	850	320	272	6	Negative
6	426	640	273	8	2 ulcers on the greater curvature, gastritis and duodenitis

* Four controls were used in this study. These animals were injected with an equivalent amount of the beeswax mixture devoid of morphine. All were sacrificed at 48 days. The upper gastrointestinal tract was negative in each instance.

the dosage of morphine most apt to produce ulcer. The minimum lethal dose of morphine for the guinea pig is 700 milligrams of an aqueous mixture hypodermically (58).

The injections of the morphine in beeswax mixture were made every evening at 5:00 P.M. If food remained in the cages at the time of the injection, it was removed until the feeding period at 9:00 A.M. the following morning. Injections were made under the loose skin of the back in multiple sites. A fresh mixture was prepared daily in 1 cubic centimeter tuberculin syringes. The diet consisted of lettuce, cabbage and "pills". Water was allowed at all times. The results are recorded in Table I.

Four of the six guinea pigs ($66\frac{2}{3}$ per cent) revealed positive upper gastrointestinal findings consisting of erosions, ulcers or a gastro-duodenitis. The most pronounced lesions were obtained in guinea pig No. 3 receiving 80 milli-

grams of morphine sulfate per kilogram of body weight. Experimental animals Nos. 1 and 2 on smaller doses of the drug survived the longest. Ulcers were not observed in either of these two latter instances. The possibility of a tolerance of the gastric secretory response to prolonged morphine administration was suggested by this observation.

In man, generalized tolerance to prolonged morphine administration is a well recognized fact. Further, tolerance of specific body systems also occurs. There is no experimental evidence available concerning the possibility of a tolerance of the gastric secretory response following prolonged morphine administration in animals. In rationalizing the evidence of tolerance as it occurs elsewhere in the body, the concept was fostered that one might anticipate the existence of such a state in the animal's response to gastric secretion.

TABLE II

All guinea pigs received 40 mgm./kilogram of body weight

GUINEA PIG NO.	WEIGHT	DAILY DOSAGE OF MORPHINE SULPHATE	SURVIVAL	RESULTS
	grams.	*mg.*	*days*	
1	1015	40.8	20	Moderate gastritis
2	530	21.2	42*	Negative
3	610	24.4	19	Moderate antral gastritis
4	640	25.6	*51	Negative
5	470	18.8	20	Large ulcer on lesser curvature; antral ulcer 1 x 1.5 cm; small one on greater curvature. Few pinpoint submucosal hemorrhages
6	560	22.4	20	Slight duodenitis (not confirmed by microscopic study)

* Survival period includes the 14-day interval during which no injections were given. Four controls were also negative.

Therefore, in a second series of six guinea pigs morphine, 40 milligrams per kilogram, was injected daily in the same manner. Injections were carried out for twenty days. Then, a fourteen-day period without injections was allowed to elapse. Following this free interval, daily injections were restarted. In this manner, it was hoped that any "addiction" and tolerance in the gastric secretory response would be broken, and a maximal gastric secretory response would again be obtained.

Only one of the guinea pigs, No. 5 (16.6%), revealed a definite "peptic" ulcer. Guinea pigs Nos. 1, 3, 5 and 6 died within the initial twenty-day injection period. The injections were discontinued on the two surviving guinea pigs, Nos. 2 and 4, for fourteen days. After this period had elapsed, injections were restarted. Neither guinea pig exhibited any gastro-intestinal pathology (See Table II).

In the first series of guinea pigs, guinea pig No. 3, receiving 80 milligrams of morphine sulfate per kilogram, developed three gastric ulcers. This dosage was considered the optimum dosage necessary to produce ulcers with morphine sulfate. Consequently, a third series of six guinea pigs was studied in the same manner previously described. All guinea pigs received the same dosage of morphine, namely 80 milligrams per kilogram. In conjunction with the injection, either a tibia and fibula, femur, humerus or radius and ulna was fractured under ether anesthesia every six or seven days. At this time we were interested in the relationship of fracture to ulcer formation (40, 41, 63, 65). It was felt that the combination of these two agents might produce a multiple stimulation effect with results more marked than with either agent alone.

Morphine injections daily and fractures at weekly intervals were carried out for a twenty-six-day period. Both injections and fractures were discontinued for a twenty-one-day period, then restarted on the same schedule. In Table III, the number of survival days includes the twenty-one-day period during which the guinea pigs received neither morphine nor fracture.

Guinea pigs No. 1 and No. 2 died three days after both the morphine injections and the fractures had been temporarily discontinued. After a twenty-one-day interval during which time neither morphine injections nor fractures were carried out, three animals, guinea pig No. 3, No. 4 and No. 5, were still living. These animals were then restarted on daily morphine injections and fractures at weekly intervals on the same schedule as previously described. In this group, guinea pig No. 5 revealed a perforated gastric ulcer, the most severe lesion encountered with prolonged morphine administration. Guinea pig No. 6 died shortly after the initial fracture was performed and probably should not be included in this series. Excluding this latter animal, gastric ulcers were present in forty per cent of the animals, i.e., two out of five guinea pigs.

Next, a series of eight cats (including three controls) was studied. These experiments on cats were identical to the previously described series of guinea pigs. Morphine sulfate in beeswax mixture was again used. The formula was altered so that 1/100 cubic centimeter of the material contained 4 milligrams of morphine sulfate.

The cat is apparently more sensitive to morphine than is the guinea pig. The minimum lethal dose for the cat is 400 to 800 milligrams of aqueous morphine sulfate injected hypodermically (59). All of the cats in this first series received 20 milligrams of morphine sulfate per kilogram of body weight, a dosage somewhat smaller than that given the aforementioned series of guinea pigs. The results are tabulated in Table IV.

Only one cat (No. 3) exhibited rather severe gastric pathology. This animal also survived the longest period of time. It was decided to study another

TABLE III

All guinea pigs received 80 milligrams of morphine sulfate/kilogram of body weight

GUINEA PIG NO.	WEIGHT	DAILY DOSAGE OF MORPHINE SULFATE	NUMBER OF FRACTURES	SURVIVAL	RESULTS
	grams	*mg.*		*days*	
1*	840	67	4	29	Two gastric ulcers, one on greater curvature; the other near the esophagus
2†	900	72	4	29	Negative
3	550	44	7	68	Mild gastritis (not confirmed on microscopic examination)
4‡	470	38	7	69	Negative
5	590	47	9	81§	Perforated ulcer on greater curvature with severe adhesive reaction in the surrounding tissue. Mild gastritis
6	680	54	3	16	Negative

* Pregnant; delivered 3 guinea pigs one day after the beginning of the experiment; no ulcers were found in the offsprings. The dosage of morphine was not changed.

† Pregnant; delivered 4 guinea pigs six days after the experiment was begun; no ulcers noted in the young; dosage unchanged.

‡ Pregnant; delivered 1 guinea pig 59 days after the inception of the study; no ulcer in the stomach of the offspring; dosage unchanged.

§ Sacrificed.

TABLE IV

All cats received 20 milligrams of morphine sulfate in beeswax per kilogram of body weight

CAT NUMBER	WEIGHT	DAILY DOSAGE OF MORPHINE SULFATE	SURVIVAL	RESULTS
	kilograms	*mg.*	*days*	
1	3.6	72	16	Negative
2	2.6	52	19	Negative
3	2.2	44	34	Multiple gastric ulcers with localized gastritis (all high on the greater curvature), one small antral erosion
4	2.4	48	17	Negative
*5	1.6	32	1	Negative
6	1.5	Controls received a comparable amount of beeswax and mineral oil. Sacrificed at 55 days.		All were negative
7	1.4			
8	2.7			

* This cat died of a severe distemper and should not be included in the analysis of this study.

group of cats using 10 milligrams of morphine sulfate per kilogram of body weight in the hope that life would be prolonged with a higher incidence of positive results. See Table V.

Cats Nos. 13 and 14 died during the night. The presence or absence of gastroduodenal pathology could not be ascertained due to the autolysis of the tissue. Only three cats can be analyzed accurately.

Cat No. 15 revealed gastroduodenal ulcerations. Cats Nos. 12 and 16 exhibited a definite gastritis which was confirmed by microscopic study. It is difficult to explain the failure to prolong life with the smaller dosage used as was anticipated.

Therefore, in both guinea pigs and cats, punched out ulcers can be produced in the upper gastro-intestinal tract with morphine sulfate in beeswax. Our

TABLE V

All cats received 10 milligrams of morphine sulfate in beeswax per kilogram of body weight

CAT NUMBER	WEIGHT	DAILY DOSAGE OF MORPHINE SULFATE	SURVIVAL	RESULTS
	kilograms	*mg.*	*days*	
12	2.7	27	18	Mild gastritis and duodenitis
13*	1.8	18	21	Post-mortem digestion of gastric wall, unable to determine the presence of pre-mortem pathology
14*	2.3	23	18	Post-mortem digestion of gastric wall, unable to determine the presence of pre-mortem pathology
15	2.3	23	9	Antral ulcer with a hemorrhagic base; punched out duodenal erosions
16	2.1	21	10	Moderate gastritis

* These cats should not be included in the analysis of this series.

experiments with pouch dogs suggest that the basis of this pathology may be related to the increased acid secretion of the stomach.

SUMMARY

In guinea pigs morphine sulfate in beeswax with various dosages, the incidence of mucosal lesions in the upper gastro-intestinal tract varied from 16.6 per cent to 66 per cent.

The combination of morphine sulfate in beeswax and fractures of long bones at weekly intervals resulted in a perforated gastric ulcer in one of five guinea pigs.

Of four cats receiving 20 milligrams of morphine sulfate in beeswax, one developed gastric ulcers. In a series of five cats receiving 10 milligrams of morphine sulfate in beeswax, the results could be correctly evaluated in only three. All three cats developed gastric ulcer and/or gastroduodenitis.

(References will be found at the conclusion of Part IV.)

PART III. THE QUESTION OF TOLERANCE IN THE GASTRIC SECRETORY RESPONSE OF POUCH DOGS TO PROLONGED ADMINISTRATION OF MORPHINE SULFATE

The probability of a tolerance to morphine with reference to the gastric secretory response has been mentioned earlier as a possible explanation for the failure to produce peptic ulceration in a larger number of experimental animals. In order to establish the presence or absence of this situation, chronic morphism was established in pouch dogs.

In the literature there are available pertinent articles relative to the production of chronic morphinism in dogs (12, 47, 48, 49, 60). These investigators have concerned themselves mainly with the general symptoms and behavior during addiction and withdrawal and the tolerance to the depressant effect of this drug. A satisfactory procedure was reported by Plant and Pierce. A similar plan was adopted in studying two pouch dogs in order to determine the presence or absence of a tolerance of the gastric secretory response to prolonged administration of morphine.

Dog #18 (weight 21.6 kilograms), a Pavlov pouch dog, was injected three times daily beginning with 7.5 milligrams of aqueous morphine sulfate subcutaneously. This dosage subsequently was increased to 15 milligrams three times daily. These injections were carried out for 27 days. A 19 day interval without injections was allowed to elapse in order to break any tolerance which might have developed. Then injections of morphine sulfate, 7.5 milligrams, were restarted for a 17 day period.

Dog #15 (weight 27.3 kilograms), a Heidenhain pouch dog, daily was injected with morphine sulfate in beeswax. This material was prepared in the usual manner, and contained approximately 200 milligrams per cubic centimeter (actually 200.74 milligrams). This mixture was prepared daily. The injections were made intramuscularly in multiple sites. For twelve days 5 milligrams of morphine sulfate per kilogram of body weight was injected. This dosage then was increased periodically until 30 milligram per kilogram of body weight of morphine was injected daily. This dosage was computed on the original weight of the animal. The criteria for increasing the dosage was based on the gastric response, the maintenance of his weight and the general well-being of the animal on the dose administered at the time of the increase.

Throughout this period of approximately two months, an attempt was made to collect the pouch secretions of both dogs for a five-hour period every other day. This was not always possible. Each hourly sample was collected in a clean test tube, measured, and analyzed for free acid and total acid in the manner alluded to previously. Food pans were removed every day at 5:00 P.M. Water was allowed up to, but none during, the test period. On the days be-

tween test days, a subcutaneous injection of one liter of normal saline was administered in addition to the morphine injections. Both dogs were weighed before each test period. Other factors pertinent to these experiments will be noted in the subsequent presentation.

The experiment with dog No. 18 was begun on May 21st. A one-hour fasting sample was obtained from 9:00 to 10:00 A.M. Then, morphine, sulfate, 7.5 milligrans, was injected subcutaneously. Pouch juice was collected for three subsequent hours. Between the third and fourth hours after the initial injection, an identical dose of morphine was administered (1:00 P.M.).

Then a one-hour sample of secretions was collected. Following this the dog was released, and removed to his cage, at which time he was fed. The last injection of morphine, 7.5 milligrams, was made at 5:00 P.M. This schedule of injections also was maintained on days during which no juice was collected. See Chart #1.

Several important points should be noted. The gastric secretory response in both acid and volume on May 21st, with morphine sulfate, 7.5 milligrams, was a moderate stimulation effect. On June 2, after the dosage had been doubled to 15 milligrams, an increased response was observed. Some increase in the amount of secretion also occurred. However, beginning on June 10th, a decrease in the gastric secretory response involving both acid and volume could be observed. Finally, on June 16th, there was a negative secretory response to 15 milligrams morphine sulfate. At this juncture a free interval of 19 days without injections was allowed to elapse. In retrospect, it would have been wiser to continue with this dosage a few more days in order to see if this negative response would be reproduced. The absence of any untoward effects, particularly vomiting, suggests that some generalized tolerance to the morphine existed.

On July 6th, injections were resumed. The dosage used was 7.5 milligrams of morphine sulfate, the same dosage used initially. A strong stimulatory response to the drug was evident until July 14th. At this time a diminution in the effect could be observed once again. This decrease progressed until only a minimal stimulation response occurred on July 22nd, when the experiment was concluded.

Dog No. 15, a Heidenhain pouch dog, was subjected to an experiment similar in all respects to that of Dog No. 18 previously related. There were three exceptions, however: (1) the dosage was computed on the basis of body weight; (2) the drug was administered daily throughout the test without any period free of injection; (3) the morphine sulfate was prepared in beeswax. The first injection of 5 milligrams of morphine sulfate per kilogram was made on May 21st. This represented 0.68 cubic centimeters of the morphine sulfate in beeswax mixture. The entire amount was injected after an hour's sample of "fasting"

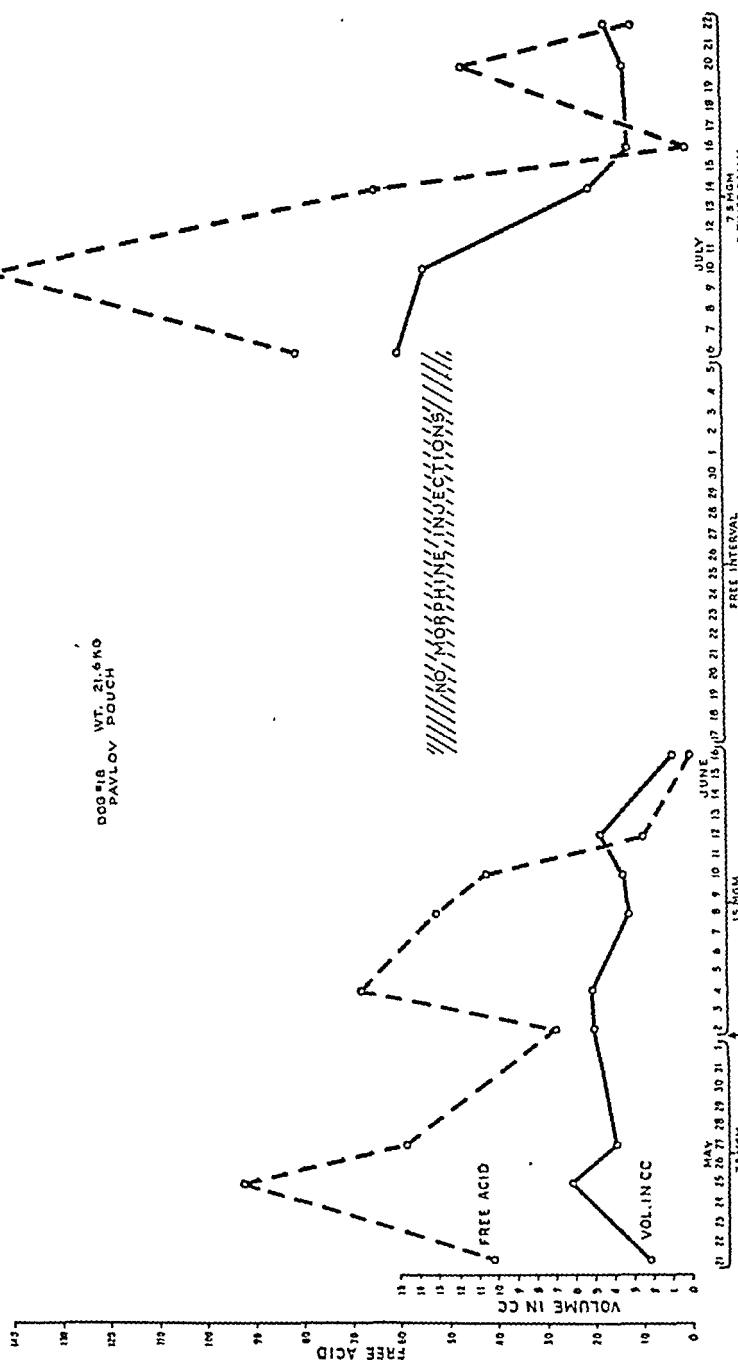

CHART 1

CHART 1. The values for free acid and volume represent the average hourly response of the animal on the day it was tested (see text).

pouch juice had been collected. Subsequently, when this dosage was doubled, the total daily dose was divided equally into two parts. The first injection was made at the usual time after the one-hour fasting sample was collected. At 5:00 P.M., when food pans were removed, the second injection was made.

A clearer conception of this experiment can be gained by inspection of the schedule followed:

Dog. no. 15. Heidenhain pouch dog, weight 27.3 kilograms

DOSAGE OF MORPHINE SULFATE ON BASIS OF BODY WEIGHT	NUMBER OF DAYS INJECTED	NUMBER OF INJECTIONS EACH DAY	TOTAL DAILY DOSAGE INJECTED
mg./kilogram			*mg.*
5	12	1	136.5
10	19	2	273
20	9	2	546
30	21	2	819

See Chart 2.

Summarizing this experiment, we note that at the beginning of the injections on May 21st, with 5 milligrams of morphine sulfate per kilogram of body weight, no stimulatory response existed for several days. However, with the increase of the dosage to 10 milligrams/kilogram, a strong stimulation of acid and volume occurred on the second day of administration. This response continued for approximately twelve days, at which time a decreased response became evident. Consequently, on June 21st, the dosage was again doubled to 20 milligrams of morphine sulfate per kilogram of body weight. The following day and for four subsequent days, the response was one of strong stimulation. This stimulation response to the increased dosage then diminished and tapered off. Therefore, on June 30th, a dosage of 30 milligrams per kilogram was begun. No unusual response occurred this day. However, for the following four days a moderately strong stimulation effect of acid and volume occurred. Again the response decreased in intensity until by July 16th the response was of no real significance.

Vomiting occurred occasionally but not regularly, during the first week of injection. This was accompanied by anorexia and some weight loss. After this initial loss the animals' weights remained fairly stationary. Listlessness was manifest throughout the experiments. Both dogs tolerated the injections without undue struggle. Certainly, there was no apparent desire for the administration of the drug. Constipation, especially with dog No. 15, was marked. Salivation was not observed; however, this symptom was not especially looked for. No significant toxic symptoms were noted in either dog. At the conclusion of the experiments both dogs were in good condition. The drug was withdrawn abruptly. No real withdrawal symptoms were evident.

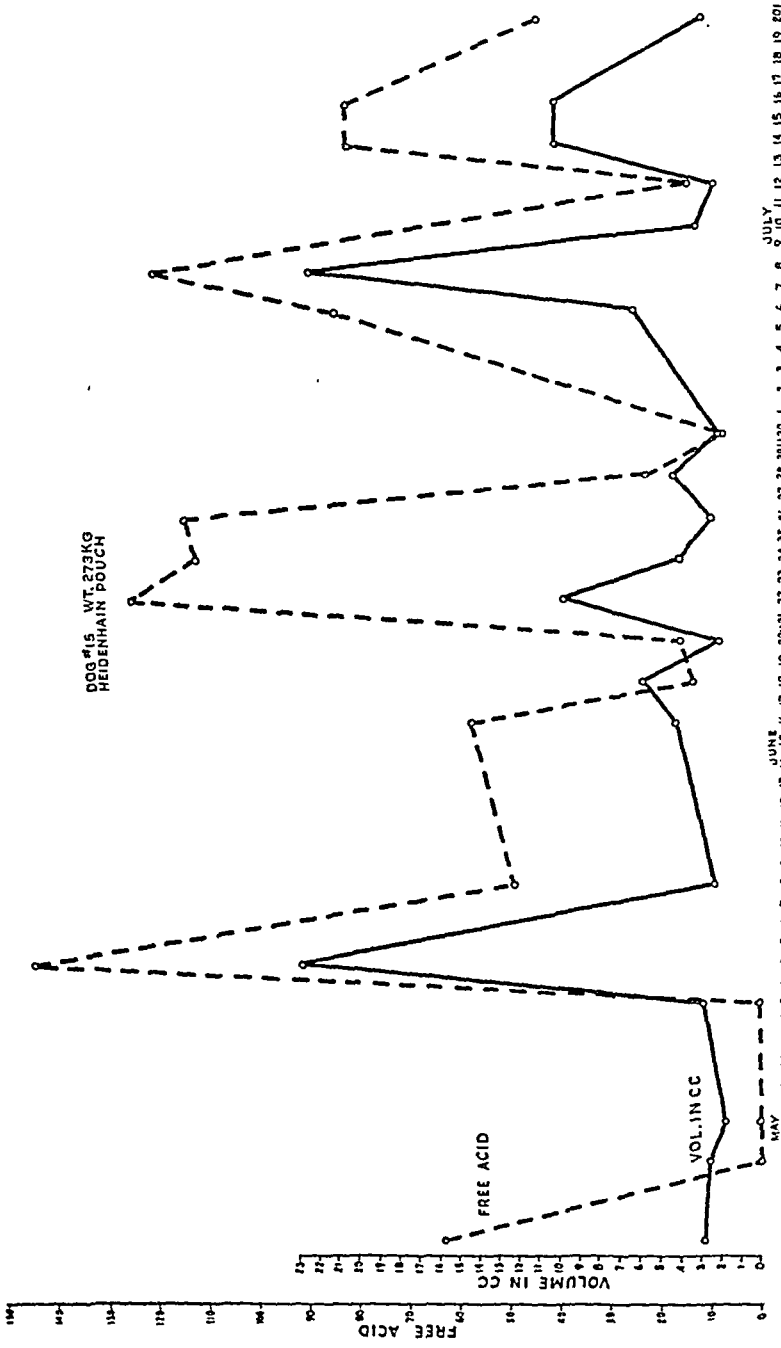

CHART 2. The values for free acid and volume represent the average hourly response of the animal on the day it was tested (see text).

SUMMARY

In order to evaluate the possible existence of a tolerance to the gastric secretory response to prolonged administration, chronic morphinism was created in two dogs; a Heidenhain pluch dog and a Pavlov pouch dog.

It was noted that the pouch acidity and volume tended to decrease gradually with the same daily dosage of morphine. With each increase in dosage, an increase of acid and volume reappeared. In one pouch dog, following a period free of injection, the same morphine dosage used at the beginning of the experiment once again elicited a response of the pouch secretory response comparable to the initial response.

These experiments tend to support the thesis that in addition to the general tolerance developing with morphine there develops also a decreased secretory response of the isolated gastric pouch.

(References will be found at the conclusion of paper IV.)

PART IV. THE EFFECT OF OPIUM ALKALOIDS AND AN "ALLIED" DRUG DEMEROL ON GASTRIC SECRETION IN MAN

In the previous work, it was observed that most of the opium alkaloids stimulated pouch secretions in dogs. Further, that "peptic" ulcers could be produced in guinea pigs and cats utilizing these drugs. If these same effects were obtained in man, certain worthwhile facts might be established which would be of aid in the medical management of patients with upper gastro-intestinal disease. Studies were carried out in man with these same drugs in order to evaluate their effect on the human secretory mechanism.

METHOD OF STUDY

Controls. In order to establish a base line whereby comparisons might be made with the results of subsequent tests, a control series of twenty-seven patients between seventeen and sixty-five years of age was studied by the intubation method. Known or suspected achlorhydrics were avoided. Patients with inflammatory diseases were omitted also. No patient was tested postoperatively. Further, no drug addicts were included in this study. The procedure followed was identical in all respects to that utilized in the subsequent tests with specific drugs. After two one-half hourly fasting samples were obtained, one cubic centimeter of sterile physiological saline was injected hypodermically. One-half hourly specimens were collected for a two hour period. This method as carried out in later experiments for collection of the specimens, measurement of the volume, and titration of free and total acid was adhered to throughout.

Five patients of this group of twenty-seven failed to secrete any free acid during the test period; they were excluded from the control group.

An average value of the free acid and volume was obtained for each one-half hourly specimen. Only the twenty-two individuals known to be capable of secreting free acid were included in this computation. In this fashion a curve was established for the free acid and volume response of the control group (Fig. 1).

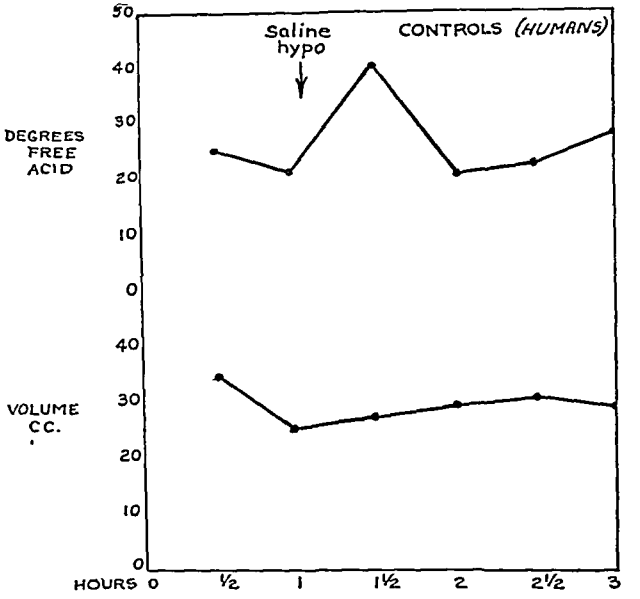

FIG. 1. These curves for both free acid and volume represent the average response of twenty-two "normal" individuals to a one cubic centimeter hypodermic injection of physiological saline. After the injection, it is interesting to note the unanticipated increase of twenty degrees in the free acid response. This curve reapproximated its pre-injection level in the subsequent specimens. The volume curve of the secretions remained rather constant.

Procedure for Testing Substances in Man.

Following a one hour control period the drug to be studied was administered orally or hypodermically and specimens were then collected every half hour for 3 hours. It was not feasible to use any individual member of the control group for testing with specific drugs.

The samples were immediately measured and titrated for free acid and total acid, using Toepfer's reagent and phenophthalein as indicators.

The graphs which appear in the text of this paper illustrate only the free acid and volume curves. In most instances the total acid curve paralleled the free acid curve being approximately 10–20° higher.

RESULTS

Morphine sulfate

The incidence of ulcer in the morphine addict. The administration of morphine to pouch dogs results in a moderate to moderately strong stimulation of pouch acidity and volume. What of the response of man to the administration of morphine?

It is apparent that on this particularly subject there is continuous human experimentation being carried out. Three institutions (one State, two Federal) were contacted that dealt with the care of hospitalized drug addicts. The opinion of the representatives of these three institutions was that the incidence of peptic ulcer in the morphine addict was not greater than that in the general average population of the same age (*10, 26, 45*). It was pointed out that "we have seen morphine addicts with peptic ulcers, but the history has usually indicated that the ulcers were present before the addiction and were a contributory factor to the addiction. It has been our experience that these patients seem to recover from their ulcers more rapidly after withdrawal from drugs."

"There is a larger group of individuals who have used drugs for the thrill of it. In this group, we have not noticed any history of the development of clinical evidence of peptic ulcer during the course of addiction." (45).

Pescor (46) in a study of 1,036 drug addicts hospitalized between 1936 and 1937 found an incidence of 11.3% of all diseases of the digestive tract; 0.9% of these were found to be peptic ulcers. The majority of patients were addicted to morphine by preference, but were intermittently addicted to other drugs.

These observations indicate that there is not a higher incidence of peptic ulcer in the morphine addict than that found in the average "normal" population. This fact does not fit in well with our experimental data with pouch dogs and smaller experimental animals. Two explanations are suggested:

1. That morphine sulfate does not stimulate gastric secretion in man or,
2. That possibly with tolerance to the drug in morphine addiction, a tolerance to the gastric secretory response occurs as well.

The experimental work with pouch dogs reported earlier would tend to strengthen the possibility of the latter contention. However, because of the possibility that man reacted differently to morphine than the dog and smaller animals, the effect of morphine on gastric secretion was investigated.

THE EFFECT ON GASTRIC SECRETION IN MAN

The gastric secretory response to morphine sulfate was studied in thirteen patients. All injections were made hypodermically. Three patients received

8 milligrams of morphine; four patients 10 milligrams; thirty patients were injected with 15 milligrams.

Morphine sulfate in 8 to 10 milligram doses evokes no significant demonstrable stimulation or depression effect on gastric secretion. The findings tend to show a depression effect on gastric acidity and volume with 15 milligrams of morphine. The depression of acidity seemed to be mild to moderate, but fairly definite. This is supported by the uniformity of the results obtained. The depression lasted for one and one-half to two hours. At this time a slight increase of acidity appears to occur. The depression in the volume of gastric secretion is more marked. The validity of considering the initial sample as a measure of the basal fasting secretion may well be questioned. The second one-half hourly fasting sample more closely approximates the basal secretion.

This depression of the gastric secretory response appeared to parallel the general depression of the mental and physical faculties of the individual being tested. The answer to the question as to why morphine addicts do not have a higher incidence of ulcer than the average individual would appear to be answered. Whereas we have observed a marked stimulation of pouch acidity and volume in dogs, the human gastric secretory response to the usual therapeutic dose appears to be one of depression.

THE PROBLEM OF SPECIES DIFFERENCE IN THE GASTRIC SECRETORY RESPONSE

The difference of the gastric secretory response in dogs versus humans is well shown. It should be remembered that no attempt was made to correlate dosage with body weight. Without further evidence, one would be unjustified in indicating a species difference. In order to answer this problem, humans should be injected with three to four times the dosage of morphine necessary to produce a gastric stimulatory response in dogs. This theoretical dosage in humans has been computed on the basis of milligrams of morphine per kilogram of body weight. (The average pouch dog weighs 20 kilograms; average human 70 kilograms.)

The injection of such a dose of morphine in a human for an experimental observation would be unwise. However, the reverse experiment is feasible. Consequently, the pouch secretory response in four dogs was studied with approximately one-fourth of the dosage which failed to produce a stimulation effect in humans.

Four pouch dogs (two Heidenhain and two Pavlov) were injected with four milligrams of morphine sulfate (veterinary) in the usual manner (see Fig. 2). In three of the four experiments a mild to moderate stimulation of pouch acidity and volume occurred. This dosage approximately equivalent to that given in man on the basis of body weight produces a stimulation effect in dogs. Man,

on the other hand, exhibits a tendency towards a depression effect. These results are rather uniformly consistent. Therefore, it appears that a species difference may exist between man and dog with reference to the gastric secretory response to the administration of morphine subcutaneously.

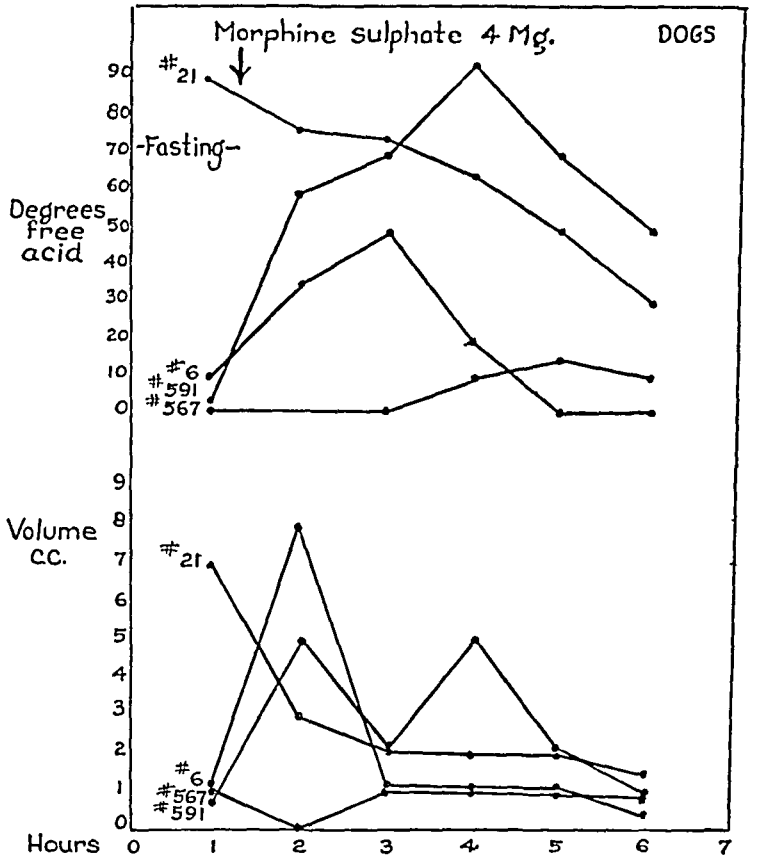

FIG. 2. Morphine sulphate, four milligrams, subcutaneously. Heidenhain pouch dogs No. 21 and 567. Pavlov pouch dogs No. 6 and 591. Dog No. 21 was fasting at 90° free acid; after the injection, there was a gradual fall of the free acid to 30°. In the remaining three experiments a mild (dog No. 567) to a moderate (dog No. 6 and 591) stimulation of free acid and volume occurred. The volume response parallels fairly well the acid response.

DILAUDID HYDROCHLORIDE

Following the same sequence of studies as were performed in dogs with isolated gastric pouches, opium alkaloids other than morphine were subsequently tested.

Dilaudid was investigated first. Seven experiments were carried out on man with two milligrams of dilaudid injected subcutaneously. No stimulation effect was observed in any instance.

PAREGORIC

Paregoric was the subject of the next series of tests. It will be recalled in the experiments on pouch dogs that this drug was a rather strong stimulator of

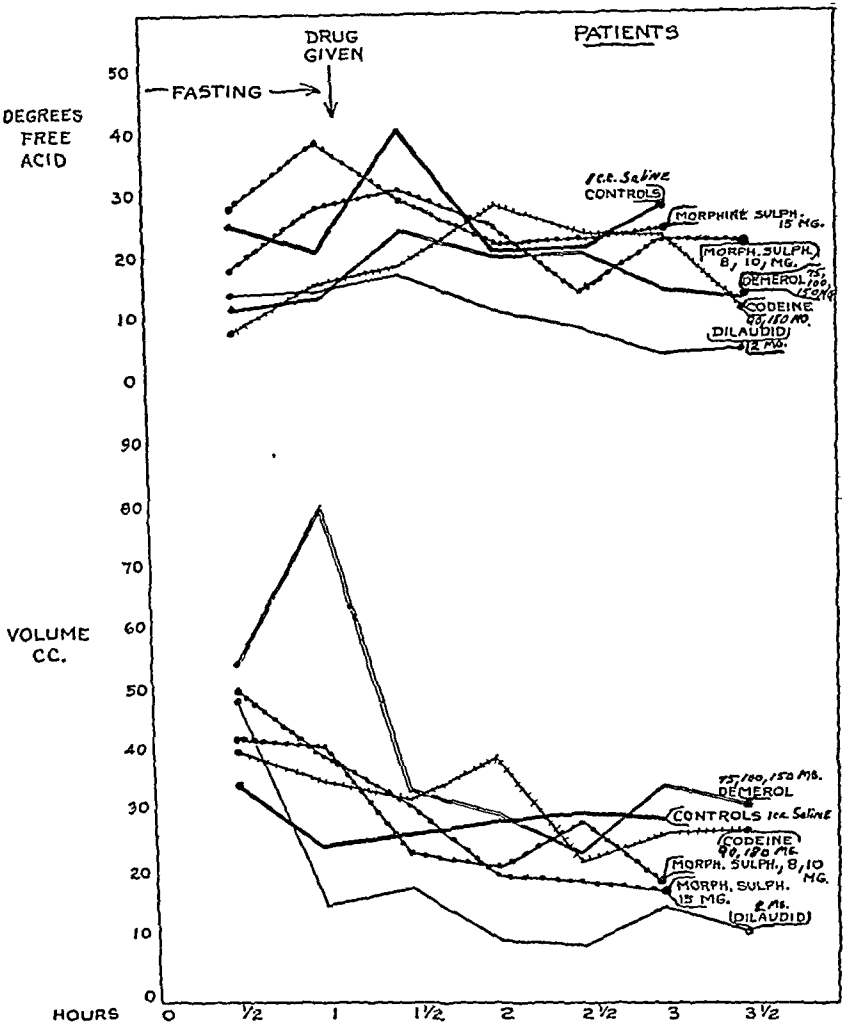

FIG. 3. These curves represent the average response of patients known to be capable of secreting free acid with the various drugs studied. The responses of the patients who secreted no free acid during the test period were excluded. This same provision was observed in the computation of the control curve. The results of the paregoric curves were not included because of the small number of valid experiments.

The level of the free acid curve tends to be depressed after the administration of morphine. However, the deviation below the level of the control group is not remarkable. The minimal depression with dilaudid is probably of no significance. Codeine produces a similar response.

The volume responses do not parallel closely the acid curves. The volume of secretion after morphine, however, exhibits a progressive decrease.

the acidity. Consequently, six tests were carried out in man. Twenty cubic centimeters of paregoric in 50 cubic centimeters of distilled water was instilled into the stomach through a stomach tube. There was no uniformity of response.

Therefore, it appears that the dosage of paregoric exerts no significant effect on the gastric secretory mechanism in man.

CODEINE SULFATE

Of all the opium alkaloids tested on pouch dogs, codeine sulfate was the only drug which failed to stimulate the pouch secretion.

Ten tests were carried out with codeine sulfate; three with 90 milligrams, seven with 180 milligrams.

Codeine sulfate in man in large therapeutic doses tends to produce a mild stimulation of gastric acidity. Certainly a depression effect is absent. Smaller therapeutic doses cause no significant fluctuation in the gastric secretory response.

DEMEROL HYDROCHLORIDE

In view of the theoretical advantages to the ulcer patient of the "combination" action of demerol and, further, because of the complete absence of any response of the pouch secretions in dogs to demerol, it was hoped that a similar response would be obtained in man.

Eight tests on patients were carried out with demerol intramuscularly and subcutaneously. One patient received 75 milligrams; five 100 milligrams and two 150 milligrams.

In six of the eight tests a mild stimulation effect following demerol administration was noted; however, one may well question the significance of this observation.

A composite graph of the average response of the human gastric secretory mechanism to the variously administered drugs has been made (see Fig. 3). The curve of the average response of patients with paregoric has been excluded. After the results of the potentially achlorhydric individuals were discarded, the number of tests was too small to be of any real value.

SUMMARY

Fifteen milligrams of morphine sulfate tends to produce a depression of gastric acidity and volume in man. Smaller dosages caused no significant deviation from the pre-administration level. A species difference appears to exist between man and dog with reference to gastric secretory response to morphine.

In man, neither dilaudid hydrochloride, four milligrams, nor paregoric, twenty cubic centimeters, produce any characteristic gastric secretory response. An equivocal stimulatory effect was noted with large doses of codeine sulfate and demerol.

These results suggest that opium alkaloid may be administered safely in the unobstructed ulcer patient without fear of potentiating the disease process.

Demerol should probably be favored in the obstructed or partially obstructed ulcer patient.

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PART V. THE EFFECT OF PHENOBARBITAL ON THE GASTRIC SECRETIONS IN DOG AND MAN

INTRODUCTION

A perusal of the literature reveals a paucity of work pertinent to the effect of the barbituric acid derivatives on stomach physiology. The essayist's interest has centered on the effect of phenobarbital and its sodium salt on gastric secretion. However, as Soma Weiss (17) so nicely puts it "all these names (allonal, veronal, luminal, etc.) are synonyms for substances which are closely related chemically in their pharmacologic and therapeutic action." Conse-

quently, the investigations on gastric secretion with drugs closely allied to phenobarbital will be reviewed.

Lundy (10) reported that with the same barbiturates, laboratory animals react in the same way as man, with the exception that in man a given dose is two to three times as effective.

Olmsted and Giragossintz (13), about the same period, described some effects of amytal anesthesia on gastric acidity and volume using the alcohol test meal and gastric aspirations. They concluded that amytal anesthesia prevented gastric secretion. Further, that in dogs so anesthetized, the stomach and intestine were practically toneless and intestinal movements feeble. This latter finding has been found to obtain also for the sodium salts of barbital and pentobarbital in experimental animals (15), including a decrease in gastric secretion following insulin hypoglycemia (8, 9).

In man, hypnotic doses of sodium amytal (0.2 grams) have been observed to decrease the emptying time of the stomach. A test meal impregnated with barium and the x-ray technique was utilized (16).

Coffey, Koppanyi and Linegar (3) 1940 reported that sodium barbital and sodium amytal intravenously, in doses of 100-250 milligrams per kilogram of body weight, produced a reduction of gastric and pancreatic secretions. These studies were made with Heidenhain and Pavlov pouch dogs. No study was made of the gastric acidity.

In 1941, Gruber and Gruber (4, 5) found in dogs that the sodium salts of amytal, ortal, pentobarbital, evipal, pentothal and thioethamyl, when injected intravenously in anesthetic doses, produced complete cessation of the action of the pylorus and stomach. Smaller doses with barbiturates decreased the height of contractions of the pylorus and stomach.

Our interest in the effect of barbiturates on gastric secretion was aroused by the observation on repeated occasions that there occurred in Heidenhain and Pavlov pouch dogs anesthetized with sodium pentobarbital (fifteen milligrams per pound) a marked depression of gastric acidity as compared to that of the dogs' pre-anesthetic state.

If man were two to three times as susceptible to barbiturates as laboratory animals (10), certain therapeutic possibilities appeared to deserve further clarification. Barker (1) in 1925 advocated the use of phenobarbital in the treatment of ulcer for the relief of pylorospasm.

METHODS OF STUDY

Experiments on dogs with isolated gastric pouches. The Method of Standardization in the fasting state alluded to previously in Part I was also used for this study. In addition, it was necessary that certain animals be standardized with histamine.

In order to test the depressant action of drugs, etc. against an artificially produced stimulation of pouch secretions, certain dogs previously standardized fasting were in addition standardized on histamine. This was accomplished in the same manner previously described with one exception. These dogs were fasted for sixteen hours in the usual fashion, after which a one-hour fasting sample was obtained. Then, 0.5 milligrams of ergamine[1] was injected subcutaneously. Hourly samples were collected for five consecutive hours. This procedure was repeated on three occasions. The free and total acid and volume were determined. An average was computed on the basis of the three separate tests.

Experiments on man. The identical method of study on man described in Part I was adhered to throughout.

RESULTS

Phenobarbital and sodium phenobarbital

Studies on dogs with gastric pouches. In the pursuit of other studies of the effect of fractures on pouch secretion (11, 12), it was observed that upon anesthetizing the animal for the operative procedure with sodium pentothal (15 milligrams/pound) the pouch secretions dropped precipitously. This fall in volume mirrored a simultaneous decrease in the acidity. Therefore, a broadening of this isolated observation was made in the following experiments.

Twenty-one experiments were performed on eleven dogs. A one-hour or two-hour fasting period was allowed. Then, the phenobarbital tablets were manually placed in the posterior pharynx. The sodium salt was dissolved in a small amount of tap water and injected subcutaneously.

Eleven of these twenty-one tests were carried out with phenobarbital. Three were carried out with 60 milligrams, five with 120 milligrams, one with 180 milligrams, two with 240 milligrams. In nine of the eleven experiments the free acid dropped to 0° in the first to fourth hours after the administration of this drug in the various dosages.

Ten experiments were performed with sodium phenobarbital. In five experiments, 60 milligrams was used; in an additional five tests, 120 milligrams was injected.

In six of the ten experiments with sodium phenobarbital, the acidity was depressed. The uniform response in both Heidenhain and Pavlov pouch dogs suggests that the effect is not mediated through the vagus. The depression effect of phenobarbital appears to be exerted directly on the parietal cells. A composite graph has been made of these results (see Fig. 1).

[1] "Ergamine" (Histamine acid phosphate) Eli Lilly Company, 0.5 milligrams of this preparation is equivalent to 0.182 milligrams of histamine base.

Effect on histamine stimulated pouch dogs. Because of the findings of a moderate depressant effect on pouch secretion with phenobarbital and its sodium salt, the following studies were made. Histamine is known to be one of the

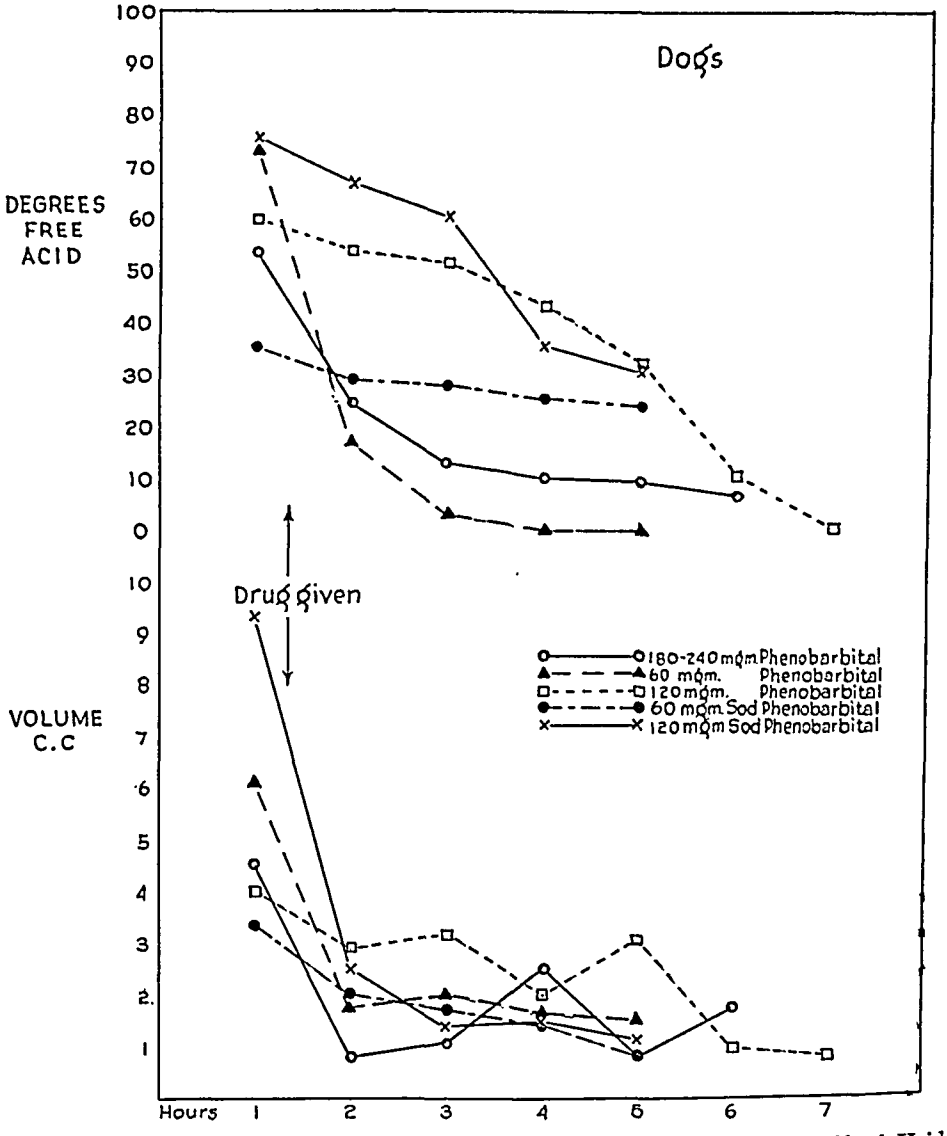

FIG. 1. This graph represents the average hourly response of free acid and volume of both Heidenhain and Pavlov pouch dogs to various dosages of Phenobarbital and its Sodium salt.

The depressive effect on gastric secretion with Phenobarbital is well demonstrated with dosages varying from 60 to 240 milligrams. In nine of the eleven experiments, the free acid fell to 0 degrees in the first to the fourth hours after the administration of the drug. The volume of secretion decreased in a parallel manner.

The results with Sodium Phenobarbital (60–120 milligrams), are not as striking, although in six of the ten experiments the acid and volume were significantly depressed.

strongest stimulators of gastric acidity available (14). The mechanism of action is directly upon the parietal cells; transection of the vagi does not affect this response (6, 7). An opportunity to evaluate the depth of the secretory

depression with phenobarbital can be made by the simultaneous administration of histamine.

Sixteen experiments were done on nine pouch dogs. Histamine standardized dogs were used (see Methods of Study). On the day of the experiment, an hour fasting sample of the pouch juice was collected. Sixty to 240 milligrams of phenobarbital or 60 to 120 milligrams of sodium phenobarbital was used. Then, 0.5 mg. of ergamine (histamine acid phosphate) was injected one to two

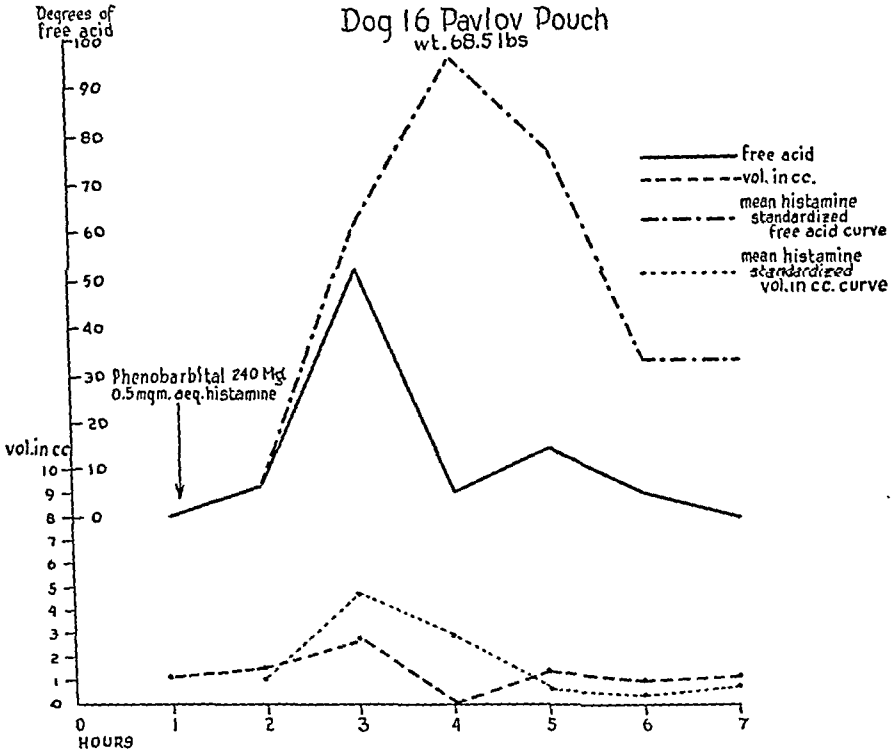

FIG. 2. Dog no. 16—Pavlov pouch dog. 240 milligrams of phenobarbital were used in this experiment. Smaller doses gave approximately the same result.

hours prior or following the administration of the drug chosen. In four experiments, the histamine and barbiturate were given simultaneously. Each hourly sample was collected in a clean test tube. All tests were terminated five hours after the last drug was given.

Uniformly, the height of the free acid curve and the duration of the curve were shortened when compared with the mean standard histamine curve of each dog. Figure 2 depicts a typical response in this type of experiment.

Figure 3 illustrates the complete suppression of free gastric acidity in spite of the injection of 0.5 milligrams of aqueous histamine. This was the only

pouch dog whose gastric secretory mechanism was completely suppressed by phenobarbital under the artificially produced stimulus of histamine.

These results also indicate that the depression effect of phenobarbital is exerted directly upon the parietal cells of the isolated gastric pouch.

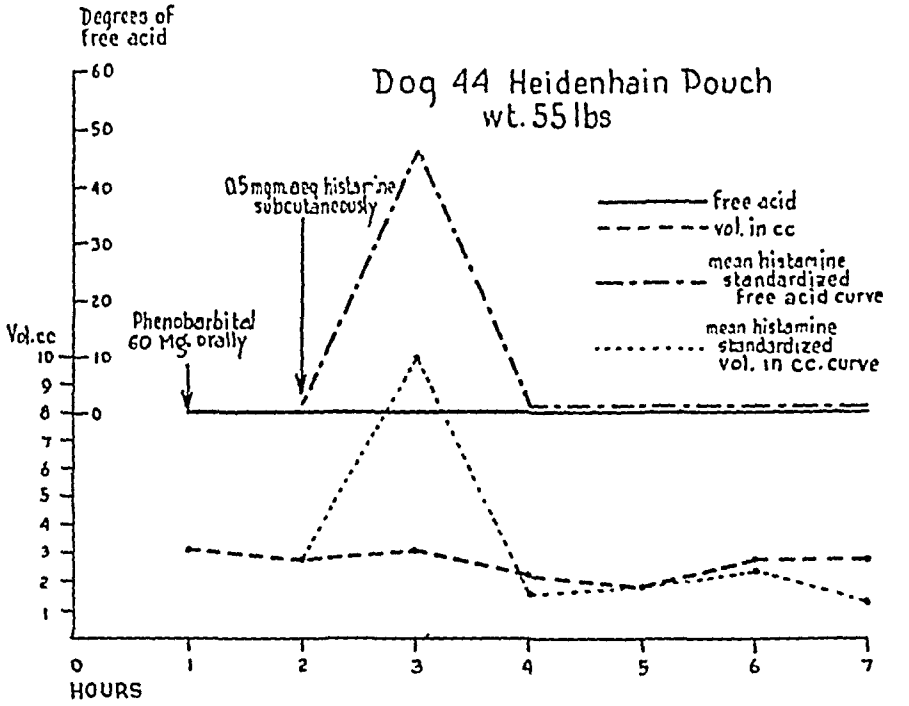

FIG. 3. This experiment was repeated with phenobarbital and sodium phenobarbital with the same result.

EFFECT IN BEESWAX ON DOGS WITH GASTRIC POUCHES

If sodium phenobarbital were able to depress pouch secretion for long periods of time, certain practical applications might be possible. The beeswax mixture of Code and Varco (2) appeared to be a satisfactory medium for the slow liberation of large amounts of this drug. Consequently, in order to test the validity of this possibility, 360 milligrams of sodium phenobarbital were prepared in 1.5 cubic centimeters of beeswax. Two pouch dogs, one a Heidenhein, the other a Pavlov, were injected into the back muscles with 360 milligrams each. No depressant effect in gastric acidity or volume was noted after seventeen consecutive hours. This failure was an attempt to investigate the possibilities of a round-the-clock depressant.

Studies on the gastric secretion in man

The experience with pouch secretions in dogs to phenobarbital and its sodium salt, fostered the hope that this drug would similarly affect the gastric secretory

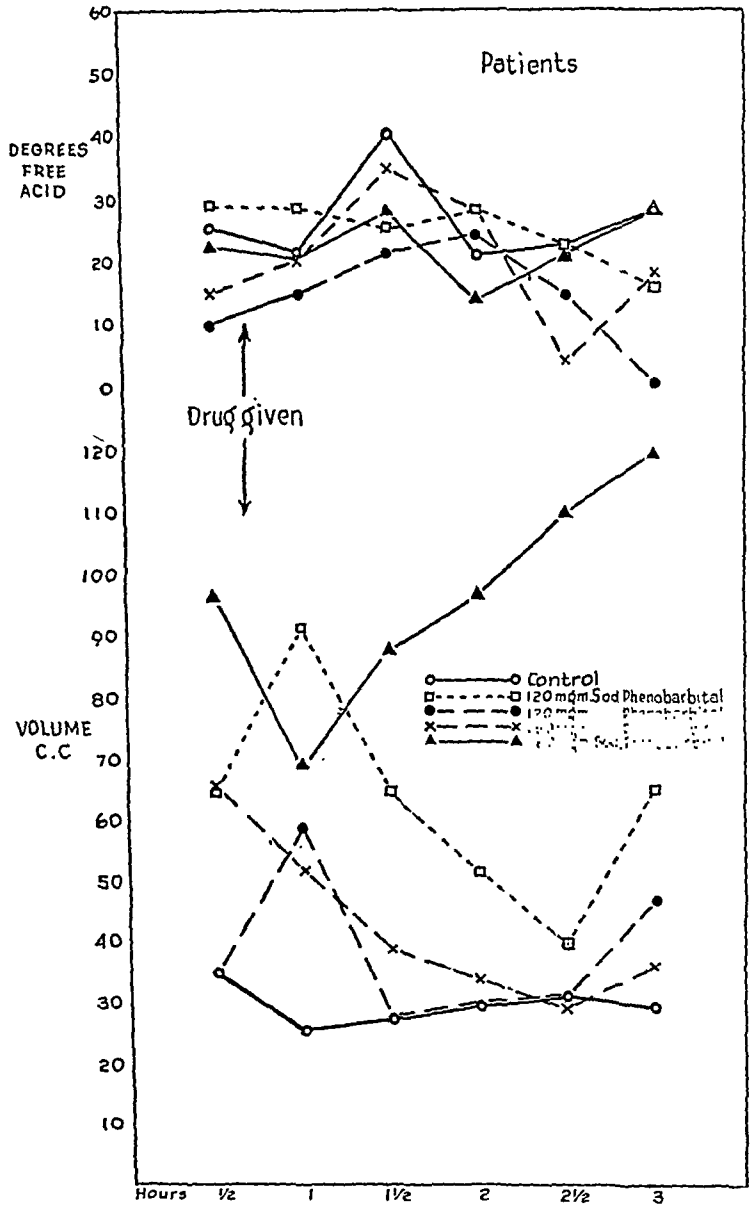

FIG. 4. This composite graph represents the average hourly response of free acid and volume in "normal" patients to various dosages (120–180 milligrams) of Phenobarbital and its Sodium salt. These curves were based on 43 individual tests.

The Phenobarbital curves suggest that a mild stimulation effect is present.

The Control curve represents a group of 22 patients injected with 1cc of normal saline hypodermically. Therefore, this curve cannot be compared with a response curve of a group of individuals given medication by mouth. However, the Control curve can serve as an applicable measuring stick with regard to the Sodium Phenobarbital curve.

The variations in the Sodium Phenobarbital curve do not appear to be significant. When compared to the Control curve, if anything, a mild depression of free acid and volume might be present.

mechanism in man. In this laboratory the ability of phenobarbital to depress pouch secretion is exceeded only by atropine. The combination of a hypnotic drug combined with an acid depressant quality would seem to be an ideal drug for the patient suffering with ulcer.

Twenty-seven tests were performed in the previously described manner. Eleven experiments with phenobarbital by mouth were done. In six of these tests, 120 milligrams were given. Five experiments were carried out with 180 milligrams of phenobarbital by mouth. A minimal stimulation effect appears to be present.

Sixteen experiments in man were performed with sodium phenobarbital: in one experiment, 60 milligrams; in eleven, 120 milligrams, and in four, 180 milligrams. All injections were made subcutaneously.

These results further substantiate the lack of any effect of sodium phenobarbital on the gastric secretory mechanism in man.

A composite graph (Fig. 4) has been made of the results obtained with phenobarbital and its sodium salt in man.

SUMMARY

Phenobarbital and its sodium salt depress pouch acidity and volume significantly in dogs. This phenomenon also occurred in histamine stimulated dogs.

Phenobarbital produces an equivocal stimulation effect on gastric secretion in man. Sodium phenobarbital appears to have no such effect.

Phenobarbital and its sodium salt may be indicated in the treatment of the patient with an obstructed or partially obstructed peptic ulcer because of their ability to decrease the emptying time of the stomach.

The stimulative or depressive effect on pouch secretion observed with this drug tested is not mediated through the vagus nerves.

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Section on
CLINICAL PATHOLOGICAL CONFERENCES
and
INSTRUCTIVE CASES

CASE OF HOUR GLASS STOMACH, GASTROSCOPY, PERFORATION OF ESOPHAGUS AND RECOVERY

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HISTORY

A 69 year old white female was admitted to the Rochester General Hospital in November, 1946 with a history of intermittent recurrent peptic ulcer symptoms during the past 28 years. Onset of the present illness began two months prior to admission. At this time she had developed, one half hour after a large dinner, a severe griping pain in the epigastric area which radiated through to the back. She experienced relief in about ten minutes following the self administration of a stomach powder. Since then she had had three similar attacks.

PHYSICAL EXAMINATION

Examination revealed a thin individual with a blood count compatible with pernicious anemia. There was moderate abdominal distension, more marked on the right side, with considerable gurgling on palpation. The liver, spleen and kidneys were not felt. A tender mass was palpated in the mid-epigastric area. Clinical impression at this time was gastric carcinoma and pernicious anemia.

X-RAY EXAMINATION

A gastrointestinal series revealed "hour glass stomach with constriction involving both lesser and greater curvatures with no element of obstruction. The duodenal cap showed a deformity characteristic of ulcer".

GASTROSCOPY

The gastroscope was passed easily into the stomach. At first a small opening was seen at the mid portion of the stomach. This was only seen once, and

then the gastroscope was passed further and the pylorus was viewed and appeared to function normally. The entire gastric mucosa as viewed appeared atrophic with stellate formed blood vessels standing out in clear relief through a very pale mucosa. The impression gained from this examination was that the hour glass deformity disappeared or was greatly minimized under the injection of air, and that the atrophic gastritis was due to the pernicious anemia.

FIG. 1

POST-GASTROSCOPIC COURSE

The patient's immediate condition following the gastroscopy was satisfactory. Twelve hours following gastroscopy she complained of a sore throat and dysphagia. Crepitus was found beneath the cricoid cartilage on the left side. A tentative diagnosis of perforated eosphagus and mediastinitis was made. Thirty six hours after gastroscopy, at which time the patient's temperature was 101 (rectal), and the pulse 100, Doctor William Farlow performed a superior anterior mediastinotomy. This resulted in the finding of a thick serosanguineous fluid of foul odor. Ten days later following penicillin therapy and drainage of the superior mediastinum the patient was on a convalescent Sippy diet.

Before discharge x-rays were taken of the thoracic vertebra with a Levine tube in the esophagus. These films failed to show any spur formation which

might have caused the esophageal perforation as a result of the gastroscope pressing the esophagus against a roughened vertebral body.

The patient was discharged in good condition on her eighteenth post operative hospital day. When last seen by her private physician a month ago she was eating five small meals a day, was in good health and had gained 15 pounds.

DISCHARGE DIAGNOSIS

1, Duodenal ulcer, 2, hour glass stomach, 3, mediastinitis, suppurative, superior mediastinum.

OPERATIONS

1, Gastroscopy, 2, mediastinotomy.

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RADIOLOGICAL CHANGES IN THE GASTRO-INTESTINAL TRACT OF A PATIENT FOLLOWING THE SMITHWICK OPERATION

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Mr. L. P., a 35 year old married truck driver, was admitted to the Hospital Central of San Luis Potosi on February 7th 1947 complaining of precordial palpitations when exerting physical effort, of four years duration; headache of mild intensity and paresthesias of the right upper and lower limbs for the last six months, and occasional transitory amaurosis and vertigo on exertion. No gastro-intestinal complaint was reported at this time.

Physical examination was essentially negative except for a moderate enlargement of the heart and a blood pressure of 225/145. Ophthalmoscopic study revealed edema of the papilla, cotton-wool patches, vascular spasm and uniform narrowing of the retinal small arteries. Orthodiagraphic examination corroborated the cardiomegaly found on percussion and demonstrated a great convexity of the left ventricular arch. EKG findings were those of left ventricular strain. Urine, blood chemistry and serologic studies were within normal limits. An intravenous pyelogram performed at this time was also normal.

The diagnosis of essential hypertension was made and a Smithwick operation was planned.

On March 14, 1947, the first stage of the Smithwick operation was performed by Dr. Clemente Robles of the Instituto Nacional de Cardiologia of Mexico City. Practically no change in the blood pressure of the patient was recorded at this time. Eleven days later (March 25) the second stage of the operation was performed and few hours later the blood pressure dropped to 160/120. A week later after an uneventful post-operative course the blood pressure was 150/100 and seven days later (April 7), the patient was discharged having no complaint and with blood pressure findings as follow: standing up 80/—, sitting down 110/90, in the recumbent position 165/130. Following this the patient returned to his usual activities, performing manual labor without complaint. Ophthalmoscopic, orthodiagraphic and EKG studies were checked and showed marked improvement. Blood pressure has been varying between 130/95 and 110/80 in the recumbent and 110/90 and 95/80 in the standing position.

The only change from his usual habits that the patient reported after the operation is that sometimes after having his breakfast he is called for an urgent bowel movement that ordinarily he is able to control but when this can not be done he has a soft bowel movement; this has attracted his attention because be-

fore the operation he always had only one normal bowel movement a day. Radiologic studies of the gastro-intestinal tract performed on May 17 showed an increase in gastric peristalisis with no organic defect of the stomach, pylorus or duodenum. Examination six hours after the ingestion of the opaque meal revealed interesting findings: there is barium retained in the stomach, the small bowel is entirely empty, the large bowel is filled with the opaque medium to the rectal ampulla; no organic defects are noticed in the intestine. The patient had a bowel movement shortly after *x*-ray examination; he noticed the presence of barium in the stool.

COMMENT

From the physiological point of view, we have to expect secretory and motility changes of the gastro-intestinal tract after the operation of Smithwick because the sympathetic supply of most of the abdominal viscera has been severed. However, to our knowledge, no report has been made of gastro-intestinal disorder following the Smithwick operation in a subject previously without digestive symptoms. Blegen and Kinter (J. A. M. A. 133, April 19, 1947), reported two cases of perforated duodenal ulcer after the Smithwick operation but their subjects had the ulcer previous to the operation.

The hyperperistalsis of the gastro-intestinal tract seen radiologically in our subject can be explained on the basis of vagotonism because of the section of the sympathetics.

The gastric stasis after six hours is an interesting finding in view of the initial hyperkinesis of the stomach.

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CHRONIC ULCERATIVE COLITIS IN TWINS

CASE REPORT

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A search of the literature since 1900 has failed to reveal any reports of chronic ulcerative colitis occurring in twins. Jackman and Bargen (1) reviewed 900 cases seen at the Mayo Clinic and found seven families with two members and one family with three members having this disease. Feder (2) reported 88 cases, with this disease occurring in two sisters. Spriggs (3) found chronic ulcerative colitis in two brothers and one sister of the same family. Bockus (4) stated, after a review of the literature, that he failed to find any evidence for familial traits or hereditary factors. "The presence of more than one case of ulcerative colitis in the same family is unusual, but there are exceptions." In view of the above, the following instance of chronic ulcerative colitis occurring in white male twins is reported. In addition to the colitis, both had hypospadias.

Case 1. C. J. B., age 17 years, was first admitted on January 20, 1941, having developed a watery diarrhea of three to four stools daily six months before, accompanied by vague lower abdominal pain. Soon after onset an exacerbation of the diarrhea occurred with fever and chills, and he was admitted to another hospital for six weeks where he improved without specific therapy. Following discharge, the diarrhea recurred with marked anorexia and rapid weight loss of forty pounds. Physical examination on admission showed an emaciated white male in no acute distress. The temperature was 38.5°C., pulse 100, and respiration 24. Blood pressure was normal. General examination was not remarkable. The abdomen was soft, without tenderness, and no organs or masses were palpable. Hypospadias was present. Proctoscopy showed only slight hyperemia of the rectal mucosa.

Hemoglobin was 9.1 Gm. (Sahli), and the red blood cell count was 3,760,000. White cell count was 12,480 and differential showed 86% polymorphonuclear forms. Stool was positive for occult blood; no parasites or amebae were seen; and stool culture showed no pathogens. Urinalysis was not remarkable. Barium enema showed marked spasm throughout the transverse and descending portion of the colon with considerable spasm about the lower pole of the cecum. The outline was very ragged and irregular. Post evacuation film (Figure 1) showed marked alteration of the mucosal outline. After preparation, including transfusion of whole blood, an ileostomy was done. Postoperatively he did well and on discharge the ileostomy was functioning satisfactorily.

He was followed as an out-patient and in 1942 it was found that the rectum was involved in the ulcerative process. On August 22, 1944 he was readmitted because of bleeding from the rectum of two hours duration. During the three year interval

he had improved symptomatically with good appetite and weight gain of ten pounds. The ileostomy had functioned satisfactorily; however each day he had continued to have per rectum one to three mucopurulent bowel movements with occasional streaks of blood. Physical examination showed the patient to be pale and poorly nourished.

FIG. 1

There was no fever and the blood pressure was normal. The abdomen was soft without tenderness. Rectal examination showed a prolapsed ring of hemorrhoids and no bleeding point could be seen. Several fissures were present. The hemoglobin was 8.1 Gm. and the remaining laboratory findings were not remarkable. Transfusions were administered and his general condition improved.

On September 8, a complete colectomy with combined abdominoperineal resection was performed. The postoperative course was uneventful with the exception of atelectasis on the sixth postoperative day, which responded promptly to treatment. After discharge, he was again followed in the clinic and his progress was satisfactory. In March 1945 prolapse of the ileostomy was corrected by operative fixation and there has been no recurrence. He now leads a normal life, being gainfully employed, and the ileostomy causes no handicap.

Pathology: Grossly, ulceration was present throughout the colon and rectum. Microscopically, extensive acute and chronic ulceration of the mucosa was seen, with frequent areas of hemorrhage. There was polymorphonuclear leukocyte infiltration of the submucosa and muscularis, subserosal edema, and early fibrinous peritonitis. The appendix was similarly involved.

Case 2. F. W. B., age 20 years, was first admitted in June 1944, because of bleeding from the rectum of four months duration. The family history was non-contributory except as noted concerning his twin. General health had been good. An appendectomy had been performed at another hospital ten months before. Six years earlier the patient had an acute illness with left flank pain, dysuria and hematuria, diagnosed Bright's disease and responding to symptomatic treatment, without recurrence. Four months earlier he had noted a large amount of clotted red blood in his stools, which lasted for one day and recurred after one month. At intervals of about three weeks, the melena recurred, lasting one to two days, and accompanied by faintness, dizziness and palpitation. He had slight cramping lower abdominal pain, but his appetite remained excellent without nausea or vomiting. Between the episodes of bleeding, the bowel movements had been regular and the stools normal. He had no other gastro-intestinal symptoms.

Physical examination showed the patient to be pale but well developed and well nourished. There was no fever or tachycardia, and the blood pressure was 178/118. General examination showed nothing abnormal except hypospadias. Abdomen was soft with slight peri-umbilical tenderness, and no organs or masses were palpable. Rectal and sigmoidoscopic examination showed nothing remarkable. The hemoglobin was 11.8 Gm. (Sahli), red cell count 3,700,000, and white cell count 9,100. Thrombocyte count was 315,000 per cubic millimeter. Urinalysis was normal. Stools were positive for occult blood on one of five examinations. Phenolsulfonphthalein test showed good excretory curve with 70 per cent total excretion in two hours. Non-protein-nitrogen was 26 mgm. per cent. X-ray studies including gastro-intestinal, ileal studies, and barium enema were normal. Exploratory laparotomy was performed and no cause was found for the bleeding. Postoperative course was uneventful and he was discharged with instructions to take iron and vitamins.

The patient was followed at frequent intervals in the clinic, having recurrence of bleeding every three to four months. Barium enema repeatedly showed no definite intrinsic lesion. He was readmitted in February 1945 because of the persistent melena. Examination was essentially as before. More complete hematological studies were all within normal limits. The stool was persistently positive for occult

blood. Kidney and liver function studies were within normal limits, except for positive galactose tolerance test. Tuberculin test 1:100 was negative. Another barium enema showed marked spasm of the cecum and lower portion of ascending

FIG. 2

colon. Transfusions were administered until the hemoglobin reached 15.2 Gm., and he was again discharged from the hospital to continue on medical therapy.

The patient was again followed in the clinic and did fairly well, although several episodes of gastro-intestinal bleeding occurred, until October 1946 when the hemoglobin dropped to 8.3 Gm. and he was readmitted. Again complete laboratory studies were done. Barium enema showed no obstruction or spasm of the colon, but

multiple small round areas were seen, which the roentgenologist felt might be due to polyps, but were most likely gas and feces. Transfusions of whole blood were given and on discharge the hemoglobin was 11.5 Gm.

The last admission was on December 22, 1946 because of rectal bleeding for twenty-four hours with passage of five stools containing clotted red blood. General examination was not remarkable. Repeated proctoscopy showed no lesions. Hemoglobin was 9.6 Gm. Roentgen studies were repeated without definite findings, although a review of all his x-rays suggested to the roentgenologist the possibility of polyposis (Figure 2).

After preparation with sulfasuxidine and whole blood, exploratory laparotomy was performed on January 4, 1947. The positive findings pertained only to the colon. From the cecum to the junction of descending colon and sigmoid, irregularly scattered

FIG. 3

areas of thickening were seen with numerous minute dilated vessels just beneath the serosa. A definite diagnosis could not be made; therefore, the cecum was isolated with packs and opened through an involved area. Three ulcers and one polypoid lesion were noted within the small segment of mucosa which could be visualized. Frozen section showed findings compatible with chronic ulcerative colitis. The colon was resected to the proximal sigmoid and an end-to-side ileosigmoidostomy was performed. His postoperative course was uneventful. Proctoscopy prior to discharge showed no lesions, although the site of anastomosis could not be visualized. Since operation, he has continued to improve, having gained ten pounds. His appetite has been excellent and bowels move twice daily. No melena has occurred and recent proctoscopy showed no lesions.

Pathology grossly (Figure 3) showed numerous irregular areas of mucosal ulceration throughout the specimen with pseudopolypi about the edges. There was one longitudinal ulceration measuring 15 cms. in length. Microscopically a chronic inflammatory process was present with large numbers of lymphocytes and plasma cells

rather densely accumulated about the innumerable ulcers. Edema and inflammatory cell infiltration had caused hypertrophied rugae to form pseudo-polypi.

Comment. Whether heredity or environment play any part as causative factors in chronic ulcerative colitis cannot be determined from one instance in twins. As the etiology remains in doubt, any information which might lead to a solution of this problem is worthwhile. For this reason, the pathologically confirmed occurrence of chronic ulcerative colitis in twins is reported.

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RECURRING MELENA IN A PATIENT WITH MULTIPLE GASTRODUODENAL LESIONS

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Presentation of Case #0-1254: The patient is a white woman, aged 47, who was referred because of gastro-intestinal bleeding.

In September, 1938, during an attack of "sore throat," the patient became faint and had tarry stools. This illness required her remaining in bed for a few days. Soon thereafter burning in the epigastrium appeared, relieved by a Sippy diet. Roentgenologic examination at that time was negative.

On November 3, 1939, the patient again was faint and had tarry stools. The family physician again placed her on a Sippy regimen with prompt relief of symptoms. There has not been a recurrence of distress since.

On January 7, 1944 during convalescence from so-called influenza, tarry stools recurred.

The roentgenologist's report on January 27, 1944 was: "Large gas bubble with pseudo-filling defect high in the stomach" (Figure 1).

Gastroscopy on February 7, 1944 showed in the proximal end of the stomach a large intragastric mass covered by mucosa having the same color and texture as the remainder of the stomach. Its outline was smooth and regular.

Surgical removal was advised.

On February 21, 1944, abdominal exploration was carried out. The pelvic viscera, colon, spleen and gall bladder were normal. There was scarring of the anterior wall of the duodenum interpreted as a healed duodenal ulcer. Through the anterior wall of the stomach a pedunculated mass without infiltration at its attachment could be palpated. It originated high on the posterior wall of the fundus near the cardia. Six or eight small lymph nodes were present opposite the base of the tumor. One of these was removed and was reported to be inflammatory.

The anterior wall of the stomach was opened longitudinally midway between the lesser and greater curves and the tumor including its base on the posterior wall of the stomach was delivered through the opening. The base of the tumor and a ring of normal-appearing surrounding gastric mucosa were removed with cautery. Infiltration of the base was not present.

The pathologist reported a leiomyoma with shallow crater, filled with exudate. There was moderate congestion of the mucosa surrounding the crater (Figure 2).

Following operation the patient's convalescence was uneventful.

The patient reported on June 13, 1946 when she was well. She was free of

digestive complaints until May 30, 1946 when after consuming a big meal of cold foods, she had a recurrence of indigestion. Distress in the region of the stomach "as if something did not move forward" was described as "almost a pain." Thereafter every three or four days there was slight pain similar to

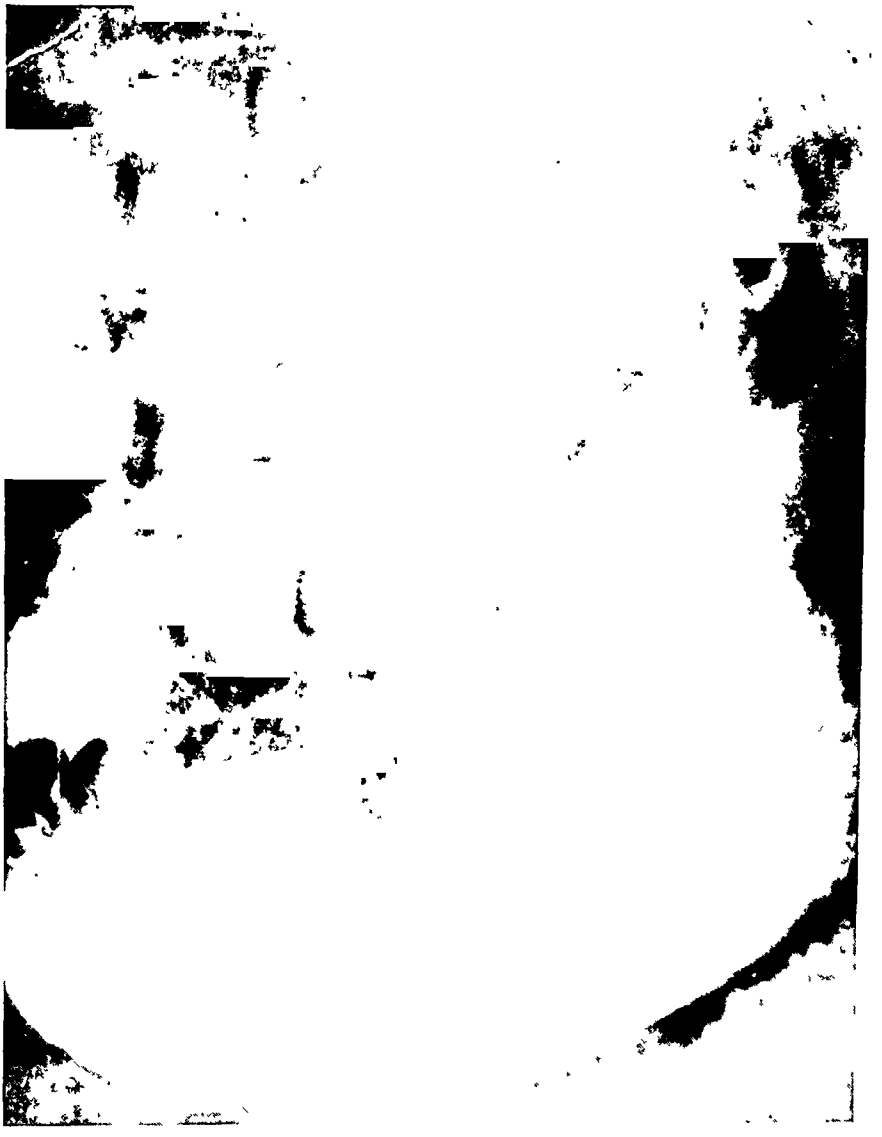

FIG. 1

that prior to operation with occasional nausea but no vomiting. The day previously the patient noted dizziness, numbness and general weakness which she described as being similar to her feeling at the time of previous hemorrhage. The stools became dark to black.

Physical examination was negative. Blood pressure: 136/84. Pulse: 124.

Positive laboratory findings included hemoglobin 12 grams, red blood cells 3,700,000. The stools were positive for occult blood. On fluoroscopy of the stomach there was hypermotility of the distal stomach with poor visualization of the duodenal cap. The crater of a duodenal ulcer was present in all the films (Figure 3).

FIG 2 GROSS SPECIMEN REMOVED AT OPERATION
Note central defect containing fibrin

Gastroscopy was performed with the following results: The usual portions of the stomach were visualized except that the pyloric antrum was transversely contracted to an elliptical channel about 1 cm. wide and 2.5 cm. long, apparently resulting from depression of the lesser curve. While peristalsis was vigorous the pyloric sphincter was not visible. The mucosa was everywhere orange-pink and slightly more pale than usual. High in the stomach was a

FIG. 3. ROENTGENOGRAM OF JUNE 14, 1946 DISCLOSING DEFORMITY OF DUODENAL CAP TYPICAL OF DUODENAL ULCER

constant band of otherwise normal-appearing mucosa extending from the posterior wall anteriorly over the greater curvature to the anterior wall. This band was normal in color, pliability and general appearance and represented

the scar which resulted from surgery. The gastroscopic impression was deformity of the pyloric antrum and body of the stomach resulting from surgery without evidence of recurrence of tumor and with pallor corresponding to the degree of anemia in the patient.

The patient was placed on a conservative program for melena followed by an ambulatory regimen and on April 10, 1947 had not had further evidence of bleeding.

DISCUSSION

This case presents the problem of recurring gastro-intestinal hemorrhage. Since the most common cause of hematemesis and melena is peptic ulcer, it is natural to assume that in a patient with typical ulcer distress, particularly if an ulcer is demonstrable by x-ray, that it is the cause of the bleeding from the upper gastro-intestinal tract. Under similar circumstances, however, multiple lesions often are present. The symptoms of ulcer may be attributable to the duodenal lesion but melena may come from a co-existing tumor or other lesion elsewhere in the gastro-intestinal tract. This possibility should suggest itself in any case wherein bleeding has occurred only as melena.

In 1934, Dudley reported a case of small tumor in the intestine with symptoms simulating peptic ulcer. In 1942, Janssen reported a case of fatal hemorrhage of peptic ulcer from the lesser curve of the stomach co-existing with fibrosarcoma of the jejunum.

The present case presents a problem somewhat in reverse of the usual order. The presenting symptom was gastro-intestinal hemorrhage which appeared during an acute illness. Subsequent to initial bleeding, distress suggestive of peptic ulcer appeared. The therapeutic test of Sippy treatment confirmed this impression. Roentgenologic examination at that time was negative. One year later the second hemorrhage appeared without distress and again the patient was placed on Sippy type of treatment. Five years later the third attack of melena appeared, again during an acute illness. On that occasion ulcer type of distress was not present. Roentgenologic examination at that time, however, disclosed a defect high in the stomach which with the aid of gastroscopy was identified as benign tumor. The tumor was removed surgically and was reported by the pathologist as benign. A deep crater at one point in the tumor was filled with partly organized blood clot indicative of recent hemorrhage. Eighteen months after the patient returned complaining of ulcer-like distress which she attributed to dietary indiscretion. On the day preceding her visit to the office she had passed tarry stools. X-ray examination performed in due course disclosed deformity of the duodenum typical of duodenal ulcer.

While it is possible that in each instance bleeding occurred from the duodenal

ulcer, it is more probable that one or more of the hemorrhages originated in the leiomyoma.

This brings up an interesting point with respect to treatment. It may be argued that since there is a tendency for bleeding duodenal ulcers to recur and since the mortality increases with each subsequent hemorrhage, surgery for duodenal ulcer now should be applied in this case. It is our feeling that a continuation of medical treatment is the proper procedure for several reasons: First, it is indicated because the most recent hemorrhage was minor in character. Second, the patient already had undergone surgery for the removal of a bleeding type of lesion. Third, aside from two attacks of ulcer-like distress which responded promptly to Sippy type of treatment and since there was no x-ray or other evidence of the existence of ulcer prior to the discovery of the leiomyoma, there is no definite evidence of the fact that hemorrhage from ulcer antedated discovery of leiomyoma. In other words, despite the fact that the patient had had several episodes of bleeding culminating in removal of a lesion having features strongly suggestive of recent hemorrhage and one which is notorious for producing hemorrhage, it may be logical to assume that only the most recent attack of melena was produced by peptic ulcer.

EDITORIAL

A POSSIBLE CAUSE FOR GALLSTONES

It is a curious fact that often men and women, given a set of facts, will for years or centuries see only one explanation for them when a little thought would have shown that the reverse interpretation was possible and even more probable.

For years anatomists have been making statistical studies of the several ways in which the common bile duct and the pancreatic duct enter the duodenum of man. According to Mehnen,[1] in 449 cases in which this part of the body was studied at necropsy, there were nineteen in which there were two papillas in the duodenum with separate openings for the two ducts. There were 151 cases in which the ducts emptied separately through one papilla. There were 248 with a common opening associated with a small diverticulum, and there were twenty-seven in which the pancreatic duct emptied into the common duct more than 8 mm. from the papilla of Vater.

In the past, practically everyone who has studied the arrangement of the ducts has done so with the thought that with certain types of anatomic construction bile might at times flow into the pancreas, there to produce an acute pancreatitis. Mehnen thought of the other possibility; namely, that in some cases pancreatic juice might run up into the common bile duct and the gallbladder, there to produce gallstones. As he said, in 61 per cent of cases there could be such a backflow of pancreatic juice into the gallbladder.

In favor of his theory is the fact that in 275 cases in which the anatomic arrangement made it possible for pancreatic juice to go back into the gallbladder there were 35.3 per cent in which gallstones were present. In the 174 cases in which the openings of the two ducts were so well separated that pancreatic juice couldn't get into the biliary tract, the incidence of gallstones was only 14.4 per cent.

Interesting, also, was the fact that in those cases with a common opening for the two ducts the characteristic sediment in the gallbladder bile contained cholesterin crystals, whereas in the persons with separate ducts, the sediment contained bilirubin concrements. It was noted also that in twenty-nine cases in which there was a strawberry type of gallbladder twenty-five had a ductal arrangement that would permit a flow of pancreatic juice into the biliary passages.

W. C. A.

[1] Mehnen, Heinz: Die Bedeutung der Mundungsverhaltnisse von Gallen- und Pankreasgang für die Enstehung der Gallensteine. Arch. f. klin. Chir., 192: 559–571 (Sept.) 1938.

COMMENT

THE PAIN OF PEPTIC ULCER

The mechanism of pain in peptic ulcer has long been a subject of debate and experimentation. A puzzling factor has been the insensitiveness of the normal stomach and intestine to mechanical trauma. Hurst (1) attributed ulcer pain to increased tension in the gastric wall. Carlson (2) and others related it to peristaltic tension similar to the gastric hunger pang. Sippy (3) maintained that ulcer pain was related to gastric acidity, being present only when "adequate free acidity" was demonstrable in the gastric content and being relieved by any measure which reduces or neutralizes the acid, such as the ingestion of food or alkali, vomiting or aspiration of the stomach.

Palmer (4) showed that in sensitive lesions the pain of peptic ulcer may be caused to reappear by reinjection of the acid chyme, whereas the introduction of gastric contents in which the free acid had been neutralized did not produce pain. Under proper conditions, typical ulcer distress could be induced by the introduction into the stomach of solutions of hydrochloric acid in physiologic concentrations (0.2–0.3 per cent), by the injection of acid gastric juice from another patient or by stimulation of the patient's own gastric secretion by means of histamine. Kymographic and roentgenographic studies indicated that, as a rule, ulcer pain was not dependent on hyperperistalsis, gross spasm of the musculature or distention of the antrum, although when the pain threshold was lowered by the digestive action of acid gastric juice, mechanical stimuli such as peristalsis and spasm might be adequate to evoke pain. The concentration of acid at the time of pain was not abnormal, nor was it greater than that present in the stomach when the ulcer had healed or was in a healing phase, indicating that the development of pain depends on the presence of a sensitive lesion as well as on acid gastric juice. Pain was thought to arise in the ulcer itself, acid gastric juice being responsible for the lowering of the pain threshold and at the same time providing the "adequate stimulus."

The recent observations of Bonney and Pickering (5) are of particular interest. In a series of 55 cases of gastric, duodenal or anastomotic ulcer and in a small number of cases of gastric cancer they repeated and amplified Palmer's experiments. They found that ulcer pain was relieved by aspiration of the stomach contents, and could be induced by reintroduction of these contents; but pain was not produced if the contents were neutralized prior to injection. Pain nearly always occurred when the gastric contents attained a certain degree of acidity for a sufficient time and was nearly always absent or subsiding when gastric acidity fell below a certain level for a sufficient time.

In the pain-free periods and in normal subjects, the introduction of acid did not induce pain. The threshold of acidity necessary to evoke pain varied greatly from one patient to another. In general, patients with duodenal ulcer had the highest threshold, those with an anastomotic ulcer the lowest, and those with a gastric ulcer were intermediate. In some cases of gastric carcinoma the threshold was still lower than that found in cases of peptic ulcer. Thus the pH necessary to evoke pain was about 1.5 in patients with duodenal and gastric ulcer and as low as pH 2.75 in anastomotic ulcer. Intragastric pressure observed during pain induced by acid solutions usually was slightly lower than that observed in the absence of pain when similar volumes of sodium chloride solutions were introduced into the stomach. X-ray examination during the period of pain revealed no localized contractions of the stomach or duodenum that were not present when pain was absent.

Bonney and Pickering also studied the time relations for the onset of pain when acid is applied to an experimentally produced ulcer of the skin. The time required for the production of pain by acid and for its relief by neutralization was found to be very much shorter than that observed in the case of peptic ulcer. The time was slightly prolonged by covering the ulcer with a thin film of mucus. When, however, the skin ulcer was protected by a scab, the time relations of the production of pain by acid and its relief by alkali were greatly prolonged, and were then of the same order of magnitude as were those observed in cases of peptic ulcer. It seems, therefore, that the time relations of pain in peptic ulcer are compatible with the chemical stimulation of pain nerve endings situated in the ulcer crater and separated from the cavity of the stomach or duodenum by a layer of functionally inert material.

These observations confirm Palmer's concept that pain in cases of peptic ulcer results from the exposure of a defective mucous membrane to a sufficient concentration of hydrogen ions, and that it is not due to general or local contraction of the stomach or duodenum.

J. B. KIRSNER

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BOOK REVIEWS

CURARE—ITS HISTORY, NATURE, AND CLINICAL USE. *A. R. McIntyre, M.D.* The University of Chicago Press. Chicago, Illinois, pp. 240, price $5.00.

Every thoughtful physician, some time in his life, must have had a desire to know more about curare, that remarkable arrow poison of South American Indians which paralyzes muscles. For years a small amount of this substance has been available for use in physiological laboratories, but until recently but little was known about the drug, whence it came, and how it was produced.

Today it is being used more and more, and some surgeons think that it is going to be the answer to one of the biggest problems in anesthesiology—namely that of securing muscular relaxation without putting the patient deeply under ether.

In this book Dr. McIntire has done a splendid job, bringing together not only the old stories of travelers in the Amazon basin but accounts of all the recent work, together with large bibliographies.

The first chapters are fascinating for any reader, lay or medical, and the later ones will be of great interest to all pharmacologists, anesthiologists, physiologists and others. The book can be highly recommended.

THE ART OF PLAIN TALK. *Rudolf Flesch.* Harper and Brothers, New York, pp. 210, price $2.50.

Here is one of the most interesting and valuable books we have ever read. It is the report of a scientific study made to determine why some writings are uninteresting, dull, and extremely difficult to read, while others are interesting and easy to read. It is curious how unconcerned most writers are about making their articles or books interesting and easily readable. As Flesch shows, even university professors will sometimes write a textbook so badly as to make it dry and almost un-understandable. The man didn't seem to care one whit whether his book was easy or hard to read. He assumed that the students would have to wade through it whether they liked it or not, so why bother to make it interesting, or to shorten the words or the sentences. On the other hand, the writer of advertising copy or the columnist or the maker of comics for the newspapers knows that if he is to hold his job and keep eating he must keep his text interesting and brief and very easy to read.

Curiously, it is in the writing of just those documents in which there should be the utmost of simplicity and clarity and the least possibility of misunderstanding that we humans pride ourselves in making a long-winded, long-worded mess of obscurity. For a good example of unreadable and un-understandable English one need only turn to the text of a treaty or a bond issue or an insurance policy or the instructions for filling out one's income tax.

As Dr. Flesch points out, some 2000 years ago St. Paul called the attention of the preachers under him to the fact that "except ye utter by the tongue words easy to be understood how shall it be known what is spoken, for ye shall speak into the air." In

other words, if a man does not say what he has to say interestingly and in a few simple words his talk will go out into the air and will influence no one; he will have wasted his time, and he will not have influenced his fellowmen as he wanted to do.

Flesch's research showed that the first requisite is to use short sentences. Standard good English has about seventeen words to the sentence; easy English will average eleven words to the sentence, while very difficult English will have twenty-nine or more words to the sentence.

The next thing to do is to use the common or familiar word instead of the rare one, the single word instead of a circumlocution, the short word instead of the long one, and often the Saxon word instead of the Romance one. Use also the word expressing something concrete and objective, instead of one expressing an abstract idea.

An important thing is to avoid the impersonal type of speech. Avoid the passive tense; to say "I performed an experiment" is much better than to say "an experiment was performed." As Flesch shows, the interest the reader gets out of a bit of writing depends partly on the number of personal references in the text: that is, references to the writer or to someone else who did something or other. Newspaper men know this trick; they always try to connect their writing with someone in their city. Nothing pleases them so much as a "local boy makes good" sort of article.

It is highly important to use words which have few, if any, affixes. The following bit of a sentence, for instance, is full of affixes, "directed to the expansion by appropriate international and domestic measures of production, employment, and the exchange and consumption of goods." Sentences full of such long words are hard to read.

One of the worst features of many articles is the inclusion of whole paragraphs which do not say anything very definite or important or understandable or based on important facts of observation. Often if an author would only allow the editor to run his blue-pencil through a half dozen of such paragraphs or pages the article or what was left of it would be read by many more men and would have much more influence on them.

Flesch points out what may not have occurred to many writers, and that is that although most persons *talk* fairly simply and intelligibly, the minute they put pen to paper they start to use another language: a bookish, stilted and unnatural language. Then they use wherever possible the longer word, or they even substitute four or five words for a common preposition.

Flesch says that most of us who write for physicians and scientists and college students are much too fearful of the chatty, simple and lucid style. We fear it is undignified, but it is not; it is natural and easy to read and understand.

Another good point which is made by Flesch and which should be kept in mind by all who write and would like to have their material read is that although most persons in the United States are technically literate, that is, they *can* read a newspaper, for them reading is such a difficult process that they cannot do it for pleasure. Hence, in the newspaper all they look at is the Funnies page. But even a man as well educated as is a physician often reads so slowly and haltingly that if he is to be reached by the printed word this word must be short and simple and chatty.

This is particularly true for the physician when he comes in from his last call at night, or what he hopes is his last call! Then, even a very rapid reader may find it almost impossible to wade into highly technical material. Only the medical writer who uses simple words can hold the attention of such a physician at nine o'clock of the evening after a hard afternoon at the office and last rounds at the hospital.

THE AMINO ACID COMPOSITION OF PROTEINS AND FOODS—ANALYTICAL METHODS AND RESULTS. *Richard J. Block, Ph.D., and Diana Bolling, B.S.* Charles C. Thomas, Springfield Illinois, Second Printing, 1947, pp. 398, price $6.50.

For years the amino acids have been of great interest to food chemists, biological chemists and physiologists, because they are the building blocks from which proteins are made. Today every physician and surgeon is interested in these substances if only because in the cases of severe inanition and protein deficiency states, mixtures of amino acids can be injected intravenously or given by mouth. This book by Dr. Block and Miss Bolling, now in its second printing, will be invaluable to all research workers in the field of dietetics and to biological chemists. It is filled with useful information.

ABSTRACTS OF CURRENT LITERATURE

FRANKLIN HOLLANDER

Associate Editor in Charge of Abstracts
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MOUTH AND ESOPHAGUS

NEUHAUSER, E. B., AND BERENBERG, W. Cardio-esophageal relaxation as a cause of vomiting in infants. Radiol. 48: 480 (May) 1947.

Persistent relaxation of the hiatus esophagus is an important but rather infrequent cause of vomiting in the newborn or young infant. The authors saw 12 cases of this type during the past 3 years. The clinical picture of persistent regurgitation that can be alleviated when the patient is placed in the erect position suggests the diagnosis.

The diagnosis can be made with certainty only by fluoroscopic examination. Retrograde filling of the esophagus during inspiration or increase in intraabdominal pressure with persistent relaxation of the hiatus esophagus is diagnostic. The condition appears to be, in the majority of instances, a temporary aberration of neuromuscular function of the hiatus portion of the esophagus and diaphragm.

FRANZ J. LUST.

STOMACH

FORSGREN, E. To what degree does gastric acidity show a tendency to rise or fall during the day? Acta Med. Scand., 128: 281 (June) 1947.

Gastric acidity after the Ewald test meal was determined at 8 A.M., noon and 6 P.M. in a large group of patients with tuberculosis. In one-third of the patients, the acid response was relatively constant for each period of the day. In the remainder, considerable variation was found. Frequently an anacid response was found in the latter part of the day despite the more or less normal acidity figures revealed by the morning analysis. A single test performed in the morning may give misleading results. At least two test meals should be given to determine gastric acidity, one on a fasting stomach in the morning and another later in the day subsequent to the strain imposed on the stomach by a meal. The author recommends that if only one test can be carried out, this should be done preferably at the time of the principal meal.

CHARLES A. FLOOD.

BRUMMER, P. On the significance of motility disturbances of the stomach as cause of gastric distress. Acta Med. Scand., 128: 338 (1947).

The author studied the incidence of motility disturbances of the stomach in patients with gastric distress. Disturbances were found in 72 of 82 patients whereas in a control group, such disturbances were only found in 5 out of 36 cases examined. Abnormalities in gastric motility were absent or very slight in patients whose gastric distress was only slight. In peptic ulcer, a distinct connection between disturbed motility and distress was observed. There was no difference in the clinical picture between different types of motility disturbances. The author is of the opinion that the immediate cause of gastric distress is a disturbance in the motility of the stomach. The term, gastric dystonia, is therefore more appropriate to describe gastric distress than is the term, dyspepsia.

CHARLES A. FLOOD.

WEGELIUS, C. Pathological gastric motility, a criterion of roentgen diagnosis in cases of gastric distress. Acta Med. Scand. 128: 349 (1947).

The author presents a scheme for the evaluation of pathological changes in gastric tonus and motility. The various patterns include normal, increased, or decreased peristalsis—in combination with normal, increased, or decreased gastric tonus. Six pathological combinations of change in tonus and peristalsis may occur, e.g., normal or increased tonus with normal peristalsis, or decrease of both tonus and peristalsis.

In comparing the presence of pathological changes of motility with the presence of gastric distress, the author found an 88 per cent positive correlation. Only 16 per cent, in a series of patients who were free from gastric symptoms, showed changes in gastric motility. This high degree of correlation between symptoms and abnormal roentgenological findings supports the view that pathological gastric motility is the primary factor in cases with gastric distress.

CHARLES A. FLOOD.

STATE, D., VARCO, R. L., AND WANGENSTEEN, O. H. An attempt to identify likely precursors of gastric cancer. J. Nat. Cancer Inst., 7: 379 (Apr.) 1947.

In 1945, a cooperative clinical study group was set up in the University Hospital of the Minnesota Medical School, embracing the Departments of Pathology, Radiology and Surgery, in an attempt to define some of the likely precursors of gastric cancer.

During a 16-month period, gastric analyses were performed on 1,253 patients over the age of 50. Of these, 238 were achlorhydric to 3 successive 0.5 mg. doses of histamine, 67 were achlorhydric to 2 consecutive 0.5 mg. doses of histamine, and 45 were achlorhydric to a single 0.5 mg. dose of histamine; 20 patients were found to be hypochlorhydric after 3 consecutive 0.5 mg. doses of histamine. In these groups, 2 unsuspected carcinomas of the stomach were found at operation, and 10 patients with gastric polyps were discovered. In a group of 84 achlorhydric individuals from a previous study, 5 additional patients with gastric polyps were encountered.

Seventy-nine patients with pernicious anemia were examined roentgenographically, but no gastric carcinomas were found. Of 40 patients with occult blood in the stool, 34 were submitted to X-ray examination and no unsuspected gastric cancer was found. Of 20 patients with hemoglobin values below 11.0 gm., 10 had roentgenograms of the stomach and no gastric carcinoma was demonstrated.

H. NECHELES.

COMFORT, M. W. AND KELSEY, M. P. Gastric acidity before and after the development of carcinoma of the stomach. J. Nat. Cancer Inst., 7: 367 (Apr.) 1947.

The mean gastric secretory activity in a group of 277 persons, in whom gastric cancer later developed, was already subnormal at the time of the initial Ewald test. On the average, this was 11.2 years before cancer was diagnosed. The mean gastric secretory activity in this series was subnormal as early as the third decade of life; it was even lower in the fourth and fifth decades. It is believed that atrophy of the gastric mucous membrane is a process responsible, in great part, for the depression of gastric secretory

activity before the development of gastric cancer.

H. NECHELES.

DAILEY, M. E. The role of cancer-prevention clinics in the detection of early gastric cancer. J. Nat. Cancer Inst., 7: 375 (Apr.) 1947.

The periodic examination of people in apparent health has proved a profitable method of discovering unsuspected accessible cancers. The early diagnosis of gastric cancer in such clinics depends upon the prompt use of the roentgenologic examination of the gastrointestinal tract of all persons with dyspepsia and all with diseases known to predispose to gastric cancer, such as pernicious anemia.

H. NECHELES.

SILVERSTEIN, I. S. Volvulus of the stomach complicated by peptic ulcer. Am. J. Roent. Rad. Therapy 57: 578 (May) 1947.

A case of volvulus of the stomach associated with a peptic ulcer is reported. The rotation was on its cardio-pyloric axis. The entire stomach was rotated with the greater curvature facing right and the lesser curvature and duodenum facing left. The course of the gastric folds assumed a transverse pattern in the upper third of the stomach, spiralling around the body. An ulcer niche was demonstrated at the pyloro-duodenal junction. The pathway of the stomach was also demonstrated by means of a radiopaque Miller-Abbott tube.

MAURICE FELDMAN.

BOWEL

HERRIN, R. C. The production and excretion of urea and oxygen consumption during intestinal obstruction in rabbits. Am. J. Physiol., 150: 494 (May) 1947.

Intestinal obstruction was produced in rabbits by ligation 15 cm. below the pylorus. The urea production during obstruction decreased in some animals and increased in others. Urea excretion was more or less reduced to levels below normal. Renal failure, as concluded from the rate of development, appears to be a consequence of the obstruction and not of the operation. Observations in dogs with Thiry fistula suggest that the effect on the kidney is not due to distention of the bowels. The skin of the rabbits showed evidence of cutaneous constriction indicating circulatory failure. These studies emphasize renal failure of urea excretion as the cause for the azotemia of intestinal obstruction.

ARTHUR E. MEYER.

SPELLBERG, M. A. AND OCHSNER, A. The role of trauma as a possible etiologic factor in regional enteritis. Am. J. Med. Sci., 213: 579 (May) 1947.

By means of a clamp, sections of ileum and jejunum 8 to 10 cm. long in the dog were traumatized by severe momentary compression. The animals survived, showing only 1 or 2 kg. loss in weight. Occasionally, gross blood appeared in the stools. Three to 7 months later, the bowel was examined at autopsy. The traumatized area was distorted by fibrous and omental adhesions, often giving sharp angulations. Regional lymph nodes were enlarged. Microscopic examination showed normal mucosa, an abnormal accumulation of round cells in the submucosa, with fibrosis there and in the muscularis. The lesions did not simulate those seen in human regional enteritis.

LEMUEL C. MCGEE.

SUAREZ, R. M., SPIES, T. D. AND SUAREZ, R. M., JR. The use of folic acid in sprue. Ann. Int. Med., 26: 643 (May) 1947.

Folic acid in varying doses and with different diets was used in the treatment of 50 cases of sprue; 22 of these were acute full-blown cases of the disease and the remainder old cases which had been satisfactorily maintained on liver therapy. The diagnosis was well established in all instances and complete laboratory studies were made. It was found that regular small daily doses were more effective than large single doses, and that smaller doses with a well balanced diet were more effective than larger doses with inadequate diet. With a balanced sprue diet the daily oral administration of 10 mg. should be satisfactory. Under this regimen the patients felt symptomatically better, appetites increased, diarrhea was controlled, inflammation of the tongue subsided, and the blood count approached normal. After initial improvement a dose of 2.5 to 5 mg. a day should

be adequate. The beneficial effects of folic acid on this and other types of macrocytic anemia may open a new era in the study of anemia.

J. DUFFY HANCOCK.

BACON, H. E., LINDE, S. A., AND MURRAY, F. H. Surgical treatment of lesions of the lower bowel. Rev. Gastroenterol., 14: 305 (May) 1947.

From a group of 472 cases of malignancy of the anus, rectum, sigmoid, and various portions of the colon, 435 patients were operated on and 382 were resected. Abdominoperineal proctosigmoidoscopy was performed in 236 cases, with 15 deaths; abdominoperineal excision in one stage was done in 51 cases (with 2 deaths) and in two stages in 6 cases (with 1 death). The authors feel that proctosigmoidoscopy may be employed with low mortality, decreased morbidity, satisfactory rate of survival, and excellent sphincter function. Six patients in whom the transverse colon was transplanted to the margin with hemicolectomy are included in this study.

C. WILMER WIRTS, JR.

LIVER AND GALL-BLADDER

MCKAY, D. G., SPARLING, H. J., JR., AND ROBBINS, S. L. Cirrhosis of the liver with massive hydrothorax. Arch. Int. Med., 79: 501 (May) 1947.

Between 1930 and 1945, 600 cases of cirrhosis of the liver were examined at the Mallory Institute of Pathology at the Boston City Hospital. Among these, there were only 6 cases with a massive uninfected hydrothorax (over 500 cc.) possessing the characteristics of a transudate and without any complicating condition. The fluid was bilateral in three instances, in the left pleural cavity alone twice, and in the right alone only once, although the total amount of fluid was predominantly right-sided. The specific gravity was below 1.018 and the total protein content below 4 per cent. The known duration was 2 weeks or more.

Ascitic fluid was found in all the cases, but in 3 it was much less in amount than the associated pleural collection. In 4 cases the cirrhosis was of the alcoholic type, in 1 there was acute yellow atrophy and 1 was unclassified. The level of serum albumin was low in all cases in which the determination was made, but no lower than in other cases of cirrhosis without hydrothorax.

Because the occurrence of hydrothorax during the course of cirrhosis is not common, perplexing diagnostic problems arise. In one case, the presence of rapidly recurring massive hydrothorax dominated the clinical course of the disease and the cirrhosis was regarded as a finding incidental to a clinically diagnosed but non-existent bronchiogenic carcinoma. In a second case, the final diagnosis was pleural effusion and hepatic failure, both of undetermined origin. When appropriate studies rule out other causes of massive hydrothorax, the pleural fluid may reasonably be considered to be associated with cirrhosis of the liver.

EDGAR WAYBURN.

HOYNE, R. M. AND KERNOHAN, J. W. Primary carcinoma of the liver. A study of thirty-one cases. Arch. Int. Med., 79: 532 (May) 1947.

Primary carcinoma of the liver is a rare disease. The incidence is greatest in the Orient and South Africa and is believed to be associated with the high geographic incidence of schistosomiasis and clonorchiasis. Thirty-one instances were found in 16,303 necropsies at the Mayo Clinic (0.19%). Almost all of the patients were over 40 years of age. Twenty-three were males.

The primary carcinomas arising from hepatic cells are called hepatomas and those arising from bile ductules are called cholangiomas. Twenty of the cases fell into the former and 11 into the latter category. Cirrhosis is frequently associated with primary carcinoma of the liver. It was present in 16 of the 20 hepatoma cases, but in only 2 of the 11 patients with cholangioma. It is debatable whether primary carcinoma of the liver occurs more frequently in association with pigmentary than with nonpigmentary cirrhosis.

There are no pathognomonic clinical or laboratory signs and the diagnosis is rarely made before death. The most significant signs found were emaciation, abdominal distension with ascites, abdominal pain, edema

of the ankles, jaundice, and a palpable abdominal tumor. The distinction between hepatoma and cholangioma is made histologically. Eleven of the 20 hepatomas were characterized by obvious invasion of blood vessels. The early vascular involvement is thought to cause the intrahepatic metastases so often found in hepatomas. In 21 of the 31 cases, extra-hepatic metastases were present. This occurred more frequently in the cholangiomas.

EDGAR WAYBURN.

RIGLER, L. G. AND MIXER, H. W. Cholangiography and biliary regurgitation. Radiol. 48: 463 (May) 1947.

The observation of the excretion of organic iodine compounds through the kidneys after injection into the biliary tract is recorded. Such excretion appears to occur uncommonly, being observed in 8 cases in a series of 460 cholangiograms. It is invariably associated with obstruction of the common duct. The evidence indicates that the contrast medium finds its way into the blood by regurgitation through the liver. The phenomenon of biliary regurgitation is thus further established. It is probable that the reactions following cholangiography are due to a transient bacteremia rather than to distention of the bile ducts. Therefore, in cholangiography care must be exercised to keep the injection pressure low enough to avoid the danger of regurgitating bacteria or other foreign material into the blood.

FRANZ J. LUST.

COHEN, P. P. AND THOMPSON, F. L. Mechanism of the thymol turbidity test. J. Lab. Clin. Med. 32: 475 (May) 1947.

Electrophoretic analyses of sera from normal patients and from patients with liver disease having positive thymol turbidity tests were made before and after treatment of the sera with thymol reagent. The chief change noted was a decrease in the beta globulin fraction of the supernatant after removal of the thymol precipitate. This drop in the beta globulin fraction averaged around 50 per cent in 11 patients with parenchymatous liver disease, the sera of whom had a thymol turbity of 4–14 units. The decrease was small in the single normal serum tested.

The thymol precipitates obtained from sera of normal patients and those with liver disease were examined in the electrophoresis apparatus; both were shown to migrate with the mobility of a beta globulin. Examination in the ultracentrifuge revealed the thymol precipitate to have a composition similar to that of the beta globulin fractions obtained from normal human plasma.

The authors suggest that the basis for the thymol turbidity test is a reaction of the reagent with the beta globulin fraction of serum. The fact that the beta globulin levels in the thymol turbidity-positive cases are not strikingly higher than those observed in normals suggests that this fraction has an abnormal component. This is supported by the fact that, in the normal, treatment of the serum with the thymol reagent seems to result in a much smaller drop in the beta globulin fraction than is the case in liver disease.

EDGAR WAYBURN.

LARSON, E. A., EVANS, G. T., AND WATSON, C. J. A study of the serum biliverdin concentration in various types of jaundice. J. Lab. Clin. Med. 32: 481 (May) 1947.

A direct spectrophotometric method for the measurement of biliverdin in serum or plasma is described. Employing the Evelyn photoelectric colorimeter, a transmission curve was prepared for a standard solution of biliverdin. The suitable wave length for measurement was found to be between 635 and 690 millimicrons. The 660 $m\mu$ filter was used. A calibration curve was obtained for amounts of biliverdin up to 5 mg. per 100 cc. of serum.

One hundred five observations were made on the sera of 66 patients with jaundice and also on the sera of 12 non-jaundiced patients. No biliverdin was found in the sera of any of the non-jaundiced patients or in patients with hemolytic jaundice. Significant levels were found in sera from patients with carcinomatous obstruction of the common bile duct, infectious hepatitis, cirrhosis of the liver, and nonmalignant obstruction of the common bile duct. It is thought that absence of biliverdinemia speaks against a diagnosis of jaundice due to neoplastic obstruction.

In three patients in whom the nutritional status improved, the biliverdinemia disappeared completely although there was no marked change in the total serum bilirubin.

EDGAR WAYBURN.

LESTER, L. J. Acute cholecystitis. Surgery, 21: 675 (May) 1947.

In a series of 109 cases of acute cholecystitis, special consideration was given to those showing jaundice. The criterion for this was an icterus index of 10 or more, and the presence of bilirubin in the urine with or without visible jaundice of the skin and mucous membrane. Nineteen patients (17 per cent of the series) fell into this category. The jaundiced group showed a palpable gall bladder and liver nearly twice as frequently as did the nonjaundiced. The incidence of gangrene was less than in the nonjaundiced, apparently indicating that jaundice is not necessarily an indication of severely inflamed gall bladders. Liver function tests were suggestive rather than conclusive. The common bile duct was found to be dilated in one third of the cases and this, rather than findings on palpation, was found to be the proper indication for exploration of the duct. In the vast majority of jaundiced patients with normal common ducts which were not explored, the jaundice promptly subsided and the patients remained symptom free. Jaundice in cases of acute cholecystitis may therefore, in most cases, be due to small nonpalpable stones that pass spontaneously, to inflammatory edema around the duct which subsides, or to spasm of the sphincter mechanism incident to the acute cholecystitis.

In reviewing the entire series of 109 cases it was found that one half the cases with a temperature over 102° and a white count over 15,000 showed gangrene, that stones were present in 97 per cent of the cases, and that while cholecystectomy was the procedure of choice the majority of patients having only cholecystostomy remained symptom free.

J. DUFFY HANCOCK.

BREITWIESER, E. R. Electrocardiographic observations in chronic cholecystitis before and after surgery. Am. J. Med. Sci., 213: 598 (May) 1947.

The author reviews the reports establishing a relationship between gall bladder disease and electrocardiographic changes, with or without symptoms of cardiac disease. She reports the electrocardiographic changes in 18 patients undergoing cholecystectomy at the University of Pennsylvania Hospital. Only two patients were males, the remainder females. In all but one patient gallstones were found at operation.

Half of the patients showed improvement in the electrocardiogram (principally T-waves) and this was attributed to the surgery. In 4 of the patients the tracings were unchanged, and in 3 the tracings were worse. One record could not be interpreted because of digitalis effects, another may have improved with the healing of a myocardial infarct.

It is concluded that "T-wave changes, unless associated with other indications of severe myocardial damage, should not be considered a contraindication to operation in chronic cholecystitis."

LEMUEL C. MCGEE.

WILENSKY, A. O. The pathogenic nature of the hepatic cirrhoses. Rev. Gastroenterol., 14: 331 (May) 1947.

The author suggests that Laennec's cirrhosis and the Hanot form of hypertrophic cirrhosis are primary affections of the connective tissue of the liver. The essential nature of the former is a slowly developing chronic lymphangitis in the interlobular stroma of the liver with subsequent contractions of the fibrotic scar tissue. The latter is essentially a systemic disease of the reticulo-endothelial system (a recticulo-endotheliolysis) in a group of organs including the liver, spleen, pancreas, and their associated regional lymph-nodes.

C. WILMER WIRTS, JR.

SUÁREZ, CARLOS VELASCO. Clinical diagnosis of cholesterosis of the gallbladder. Arch. argent. de enferm. d. ap. digest. y de la nutrición. 22: 75 (Mar.–April) 1947.

The author presents his experience with about 100 cases of cholesterosis of the gallbladder. The disease was found to be more frequent in obese women who had an irritable vagus nerve; the pain was of the sub-

acute type and recurred frequently. The X-rays showed a well filled gallbladder emptying very rapidly; sometimes the cystic duct and the choledochus could also be visualized. The recovery of "lipoidic corpuscles" during the biliary drainage is the most important sign of the disease, according to the author.

ALOYSIO FARIA.

PANCREAS

GLENN, J. C., JR. AND BAYLIN, G. J. The roentgen findings in acute pancreatitis. Am. J. Roent. Rad. Therapy 57: 604 (May) 1947.

The authors quote the literature on the etiologic, clinical, and laboratory findings in acute pancreatitis, and stress the X-ray signs. These include (1) enlargement of the head of the pancreas thus widening the duodenal loop, (2) flattening of the folds, (3) inverted three sign in the duodenum, (4) displacement of the duodenum, and (5) spasm of the duodenal loop.

The roentgen signs depend upon the site of involvement in the pancreas. The association of a duodenal diverticulum is emphasized as being part of the pancreatitis picture in some instances.

MAURICE FELDMAN.

ANEMIAS

MULDER, H. P. AND MULDER, W. J. Graves' disease and Addisonian pernicious anemia. Acta Med. Scand. 127: 218 (1947).

The simultaneous occurrence of Graves' disease and pernicious anemia has been described frequently in the literature. Two patients with this combination of diseases are described by the authors. Thyroidectomy was performed on both patients after treatment of the anemia. Following operation, there was no recurrence of the anemia in spite of the fact that liver therapy was discontinued. In one patient the recovery from pernicious anemia lasted for almost 2 years, and in the other case there was no recurrence of anemia for nearly 4 years. The possibility is suggested that hyperthyroidism may exert an injurious influence on the production of intrinsic factor, and that after elimination of this influence the production of intrinsic factor returns to normal.

CHARLES A. FLOOD.

BOE, J. On so-called atypical cases of pernicious anemia. Acta Med. Scand. 127: 264 (1947).

In patients with a picture suggestive of pernicious anemia who do not respond to the usual liver therapy, one is apt to doubt the correctness of the diagnosis. However, in 2 of the author's cases of pernicious anemia, an iron deficiency was present simultaneously, and both liver and iron were necessary to prevent deficiency symptoms. In 2 other cases of pernicious anemia, treatment with the usual liver extract had little or no effect but the use of a less purified extract gave a good response. The latter results are thought to be due to a lack, in these cases, of another unknown factor which is only present in low concentrations in the purified liver extracts commonly in use. In some cases in which it was difficult to raise the red cell counts above 3 to 3.5 million, the peroral administration of a stomach-liver preparation proved effective.

CHARLES A. FLOOD.

ULCER

DOUGLAS, D. M. Chronic ulcer of the stomach and duodenum. Gastroenterologia, 72: 145 (1947).

If psychological factors play any part in the etiology of peptic ulcer, one would expect to find that the results of treatment would be adversely affected by the wartime conditions in London. However, in a study of 211 cases of peptic ulcer with an average follow-up period of 6.09 years, the results of treatment compare favorably with those reported for peacetime periods. Partial gastrectomy gave much better results in gastric ulcer than either medical treatment or conservative surgery. In duodenal ulcer without stenosis, surgical therapy gave significantly better results than medical treatment. There was a high wartime rate of jejunal ulcer after gastroenterostomy. In duodenal ulcer with pyloric stenosis, the results of gastroenterostomy were usually satisfactory. No significant relationship could be found between recurrent ulcer after medical or sur-

gical therapy and levels of gastric acidity before treatment.

CHARLES A. FLOOD.

WEINSTEIN, V. A. AND COLP, R. Supradiaphragmatic vagotomy in gastrojejunal ulceration following subtotal gastrectomy for duodenal ulcer. Surg. Clinics N. Am., 249 (Apr.) 1947.

A preliminary report is made of early effects of bilateral supra-diaphragmatic vagotomy in 10 cases of gastrojejunal ulcer. It is suggested that the psychic phase of gastric secretion may have played a more prominent role than the chemical phase in the causation of ulcer in these cases. This is the rational of vagus section. Eight of the cases were done in the past year; 2 were completed seven years ago and were previously reported. Of the 8 recent cases, 5 have experienced no abdominal symptoms, and 3 are much improved. The authors emphasize the value of the Hollander insulin hypoglycemia test as an indicator of partial or complete vagotomy. In 5 of the 8 recent cases complete section was effected.

While no final conclusions can be drawn, one very impressive feature was the dramatic relief of ulcer pain, which has not returned during the limited period of observation.

FRANK G. VAL DEZ.

HOLLANDER, F. Are gastric ulcer and duodenal ulcer different diseases? Surg. Clinics N. Am., 265 (Apr.) 1947.

Factors which differentiate gastric and duodenal ulcer cases are the following: (1) Volume of secretion, in a fixed time interval, is greater in duodenal ulcer. (2) Free acidity and pepsin activity are greater in duodenal ulcer, whereas in gastric ulcer the range of variation coincides with that of normal individuals. During two-hour fractional analyses, in both gastric and duodenal ulcers, both curves rise in the three 15-minute periods, following an initial drop; thereafter, the curve for gastric ulcer falls off, but that for duodenal ulcer continues to rise to the end of the 2-hour observation period. (3) Duodenal ulcer is usually accompanied by hypertonicity and hyperperistalsis, whereas gastric ulcer is less likely to do this. (4) Gastric lesions, on the average, are much larger than duodenal lesions. (5) Pain is more intense in duodenal ulcer cases. (6) The peak age for duodenal ulcer is in the 4th decade, and that for gastric ulcer in the 5th.

The two theories proposed to account for the above differences are as follows: (1) The neural theory states that a predominant factor in the etiology of peptic ulcer is a psychosomatic one mediated by both the sympathetic and parasympathetic nervous systems. Psychic disturbances occur more commonly in patients with duodenal than gastric ulcer. (2) The duodenal theory proposed by Shay and his associates implies 1 or 2 normal inhibitory mechanisms for gastric secretion, arising in the duodenum; one involving enterogastrone, and the other a local neural factor. In the presence of a duodenal ulcer these inhibitory mechanisms are disturbed.

In conclusion, the differences in clinical manifestations between gastric and duodenal ulcer are secondary and due to the difference in location, rather than primary and the result of their being two different diseases.

FRANK G. VAL DEZ.

BRICE, P. B. AND LEE, T. F. Digestion of living tissue by the hyperacid stomach. Surg., Gyn., Obs., 84: 959 (May) 1947.

In this experimental study, it was found that living autogenous organs and tissues of all sorts are completely digested in 1–6 weeks after being deeply implanted in the canine stomach. Following implantation, the animals received daily injections of histamine mixed with beeswax and mineral oil, in order to produce a high degree of hyperacidity. Results of these experiments have been compared with those of a similar series of implantations in stomachs not stimulated by histamine injections.

Implants of intact jejunum, appendix, and cecum were quickly digested by the hyperacid stomach. In normal dogs, complete digestion of the hepatic implant was not accomplished until the end of the fourth week; however, at that time, digestion of the implants was complete, and the rate of digestion exceeded that of a normal stomach. Tissue reactions to the corrosive process were also more violent.

Only a small proportion of the animals receiving histamine developed spontaneous

ulcers at a distance from the implant, but in a control series, ten dogs receiving more prolonged histamine therapy developed gastric or duodenal ulcers. Most of the dogs receiving histamine exhibited deterioration of general health, loss of appetite, and a moderate degree of anemia. Gross bleeding from the implant was a common finding, and evidences of toxicity were pronounced during the period of digestion.

This investigation justifies the conclusion that living organs and tissues of all sorts are susceptible to gastric digestion, and that hyperacidity increases the rate of that digestion.

FRANCIS D. MURPHY.

NASIO, J. Effect of ascorbic acid upon cinchophen experimental peptic ulcer. Rev. Gastroenterol., 14: 340 (May) 1947.

The simultaneous administration of cinchophen and 500 mg. of ascorbic acid to dogs, during periods of time ranging from 15 to 22 days, prevents the appearance of the peptic ulcer in over 60 per cent of the cases. In some animals cicatrization of the ulcerous lesion has been shown. Loss of weight is greater in the control animals than in those receiving the ascorbic acid.

C. WILMER WIRTS, JR.

PROCTOLOGY

SWEET, R. H. Results of treatment of epidermoid carcinoma of the anus and rectum. Surg. Gyn. Obs., 84: 967 (May) 1947.

A study of epidermoid carcinoma of the rectum arising in the anal canal has been made from the case records of the Palmer Memorial and Massachusetts General Hospitals. Of 77 patients with epidermoid carcinoma of the anal canal and rectum observed in this study, only 13 lived five years or more free from disease. Of 48 patients operated upon radically (including both abdomino-perineal and colostomy and posterior excision techniques), 12 patients lived five years or more without disease.

Some form of irradiation treatment was used in 19 cases. Of the 7 patients given X-ray treatment, all died. The use of platinum needles or gold seeds implanted into the tumor or around its periphery was equally disappointing.

Comparing the two methods of treatment, it was concluded that, from the standpoint of cure and palliation, the surgical method of treatment was notably superior to any form of irradiation.

FRANCIS D. MURPHY.

ORTMAYER, M. Biologic characteristics of nonpalpable, nonsymptomatic, solitary polyps of the rectum. J. Nat. Cancer Inst., 7: 387 (Apr.) 1947.

This study is based upon the sigmoidoscopic and roentgenologic examination of the colons of 1,031 well women at the Cancer Prevention Center of Chicago, between April 1945 and November 1946. Ages of the women ranged from 22 to 73 years; ⅔ of them were between 31 and 56, nearly ½ between 36 and 47 years. Among these well women nearly 2 per cent were found to harbor polyps in the rectum above the anal papillae. Some were benign, some suspicious of early carcinoma, and some diagnosable as preinvasive carcinoma. The youngest woman with a polyp was 26, the oldest 61. The castor oil technique adapted from Weber's preparation for barium enema, which yields clear vision in a high proportion of patients, was used. A thorough enema preparation is less generally useful. These findings demonstrate the necessity of removing polyps completely, or else of examining biopsy specimens of these polyps carefully.

H. NECHELES.

SURGERY

HWANG, K., ESSEX, H. E. AND MANN, F. C. A study of certain problems resulting from vagotomy in dogs with special reference to emesis. Am. J. Physiol., 150: 429 (May) 1947.

Functional changes after vagotomy at various levels, from the diaphragm up, were studied roentgenologically. Frequent regurgitation and emesis were observed after vagotomy at or above the level of the hilus of the lung. These reactions were less severe when feeding was given parenterally. The most important change, after vagotomy above the level of the aortic arch, was complete loss of the peristaltic activity of the

lower part of the esophagus. The paralyzed esophagus retained food material, but neither this or the distention alone was the cause of vomiting. Nausea and vomiting were rather the consequence of irritation of the larynx by the large amount of regurgitated material. The response to appropriate doses of apomorphine was greater after vagotomy than before. Complete sympathetic ganglionectomy had no or only insignificant effects on esophagus and cardia. The peristalsis of the lower two-thirds of the esophagus is dependent on the extrinsic vagal supply. The vagus contains inhibitory and motor fibers to the cardia. When the cardia was freed from vagal control, the orifice was never increased but was reduced to different degrees in most cases.

ARTHUR E. MEYER.

ROSENAK, S. AND HOLLANDER, F. Early postoperative motor response of the small intestine to jejunal feedings. Surg. Clinics N. Am., 345 (Apr.) 1947.

Five patients with surgical jejunostomy were utilized in a study of the motor activity of the gastrointestinal tract. This investigation employed barium dispersed in 100 cc. of the pre-digested jejunostomy aliment previously described by the authors, the mixture being injected over a 5-minute interval through the jejunostomy. Several radiographs were taken to observe the course of the meal.

On the 2nd day after operation, the jejunum was completely devoid of radio-opaque aliment 5 hours after administration, in 3 of the 5 patients. The aliment was in the cecum and ascending colon by the 24th hour in all of the cases. Control values were established by repeating the studies in 3 of the patients 3–5 weeks after operation. There was generally a higher rate of propulsion at that time. The head of the meal was in the cecum by the end of the 1st hour in 2 instances; the 3rd required 3 hours to reach this level.

The aliment is transported through the bowel by active peristalsis as evidenced by segmentation in the radiographs. Retrograde movement of the aliment was not observed.

It is concluded that jejunal feeding may be instituted 24 hours after operation provided certain precautions are adhered to. Proper control of the volume and rate of administration of the aliment are most important. The feeding procedure apparently does not jeopardize the duodenal stump, as evidenced by the absence of retrograde movement of the aliment.

FRANK G. VAL DEZ.

NAFE, C. Congenital hypertrophic pyloric stenosis. Arch Surg., 54: 555 (May) 1947.

Congenital hypertrophic pyloric stenosis is the most common condition requiring surgical treatment in the infant. Heredity appears to be an important etiologic factor. The diagnosis can be established by observing projectile vomiting and strong gastric contraction waves following the use of milk cereal feedings over a short period. Roentgen examination is of doubtful value and a barium sulfate meal should be avoided except when there is an unusual problem in diagnosis. Pyloromyotomy is the treatment of choice. This operation yields gratifying results and should carry with it a low mortality if not delayed too long. Two deaths occurred in 129 infants on whom this operation was performed.

C. WILMER WIRTS, JR.

ANATOMY

DURAN-JORDA, F. Histopathology of the gastric semisquamous epithelial layer. Surg. Gyn. Obs., 84: 983 (May) 1947.

The author, having described previously the semisquamous epithelial layer which covers the normal gastric and intestinal mucosae, now outlines the different histopathological syndromes found by making a study of resected specimens of stomach. From his investigation, the author concludes that the crater of a gastric ulcer is without any protection from the semisquamous epithelium. The protective function of the semisquamous epithelial layer is demonstrated by the process of cicatrization of the ulcer. From his study, the author describes the role the semisquamous layer plays in the mechanism of healing and mucous membrane reconstruction.

FRANCIS D. MURPHY.

MISCELLANEOUS

LAGERLÖF, H. O. Stalagmometric determination of normal serum esterase and pancreatic lipase in serum. Acta Physiol. Scand., 13: 301 (June) 1947.

This paper reports the definite methods which make it possible to differentiate between the normal serum esterase and the pancreatic lipase in serum. The esterase activity of normal serum almost exclusively depends upon the activity of the normal serum esterase. This esterase is inactivated by atoxyl and is not activated by calcium oleate. Pancreatic lipase in serum is completely resistant to amounts of atoxyl which cause submaximal inhibition of normal serum esterase. Pancreatic lipase is activated at least fifty times by addition of calcium oleate. Therefore it may be determined separately from the serum esterase if the latter is inhibited submaximally with atoxyl and the pancreatic lipase is activated with calcium oleate.

ALBERT CORNELL.

LAGERLÖF, H. O. Normal serum esterase and pancreatic lipase in diseases outside the liver, the biliary ducts and the pancreas. Acta Med. Scand. 128: 380 (1947).

In a series of normal individuals, the normal serum esterase was found to range from 4.3 to 63 in women and 17 to 66 in men. Pancreatic lipase varied in normal persons from 0.77 to 2.9. The normal serum esterase was normal in 72 of 75 cases of circulatory disease, acute infectious diseases, bronchial asthma, hyperthyroidism, disease of the gastrointestinal tract, and diabetes mellitus. On the average it was high in cases of hyperthyroidism, and in one case it was markedly elevated. It was decreased in two cases of uncompensated heart failure, possibly as a result of liver damage.

The pancreatic lipase was normal in 70 of the above mentioned cases. Elevated values were observed in 3 cases of duodenal ulcer. In 1 case there was a perforation of the ulcer, and elevation of the lipase may have resulted from leakage and absorption of pancreatic enzymes. In 2 cases, the slight elevations of pancreatic lipase may have been due to spasm of Oddi's sphincter caused by opiates. In diabetes mellitus, the pancreatic lipase was, on the average, very low.

CHARLES A. FLOOD.

DEANE, H. W. A cytochemical survey of phosphatases in mammalian liver, pancreas and salivary glands. Am. J. Anat. 80: 321 (May) 1947.

Observations were made on the location of phosphatases in the liver, pancreas, and salivary glands of rodents and rhesus monkeys. The parenchyma or stroma of all 3 organs contains acid and alkaline glycerophosphatases, glucose monophosphatases, nucleic acid phosphatases, and alkaline fructose diphosphatase. All the demonstrable alkaline phosphatases are apparently secreted into bile by the liver cells and into saliva by the salivary glands. Alkaline fructose diphosphatase and neutral monoesterases appear to be universal in distribution. It is suggested, therefore, that these enzymes may be essential to the basic metabolism of tissues, irrespective of specific functions.

ALBERT CORNELL.

ADLERSBERG, D. AND HAMMERSCHLAG, E. The postgastrectomy syndrome. Surgery, 21: 720 (May) 1947.

Marginal or recurrent ulcers are not the only incapacitating conditions arising after subtotal gastrectomy. A small percentage of cases will show persistent distressing symptoms such as postprandial fullness and nausea, eructation and belching, weakness, fatigue, dizziness, constipation or diarrhea, and especially inability to gain weight and to work. Many patients showing such trends will be found to be of the psychosomatic type. Blood studies give no significant findings, and there is no correllation between the lack of gastric acidity and the occurrence of gastric symptoms. Gastro-intestinal X-rays are essentially negative. Blood proteins are usually normal, as is vitamin A serum concentration.

The early postprandial symptoms are probably caused by mechanical factors such as small stomach with rapid emptying and overflooding of the small intestines. The late postprandial symptoms are due to chem-

ical factors: e.g., hypoglycemia secondary to the exaggerated postprandial hyperglycemia, and occasionally secondary to disturbed intestinal absorption.

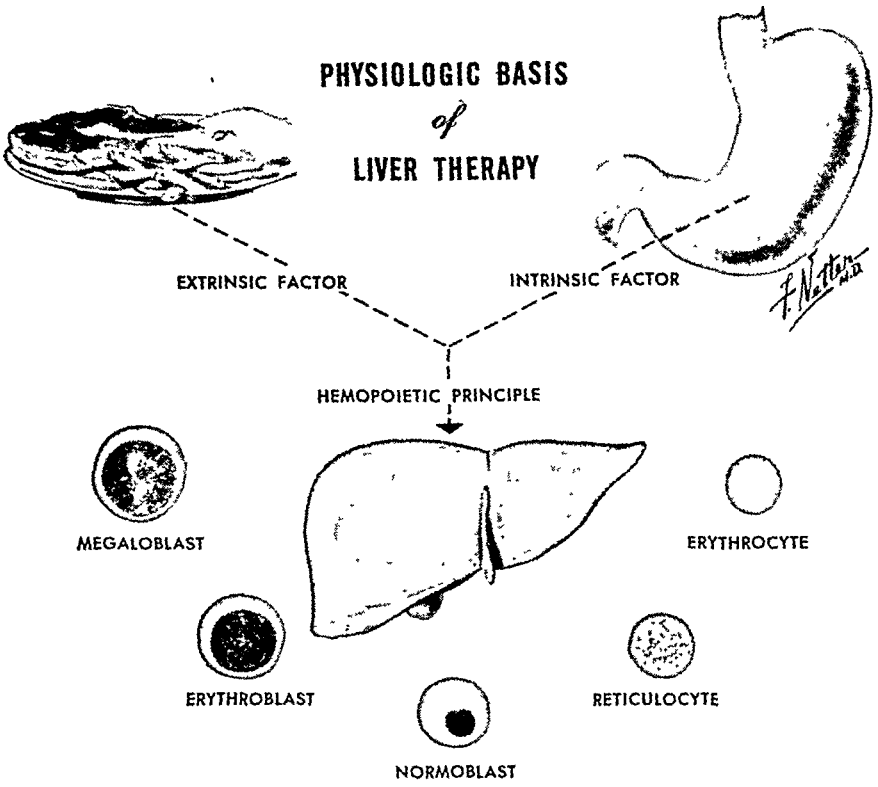
The treatment must be clinical, nutritional, and psychological.

J. DUFFY HANCOCK.

ARNETT, J. H. Treatment of carriers of endamoeba histolytica and other protozoa with carbarsone, chiniofon and vioform. Am. J. Med. Sci., 213: 608 (May) 1947.

It was determined previously by stool examination that 11 per cent of the inmates of a home for the aged, and the same per cent of the food handlers in a Philadelphia college, were carriers of E. histolytica. Administration of chiniofon (0.25 gm. 2 or 3 times daily) was followed by the disappearance of the E. histolytica from the stool in an average of 3 days in 11 of 12 subjects. The twelfth subject had negative stools after the 4th day of the second course (7 days) of the drug. Carbarsone (0.25 g. twice daily for 10 days) cleared the stools in 2 days (average) in 12 subjects. Treatment with vioform (0.25 g. 3 times daily for 1 week) was equally successful in the same number of carriers. These drugs did not show a similar effectiveness in eliminating other protozoa from the stools.

LEMUEL C. MCGEE.



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The Present Status of Vagotomy in the Treatment of Peptic Ulcer. Julian M. Ruffin, M.D., and Donald P. White, Jr., M.D.

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An Experimental Study of the Acid Factor in Ulceration of the Gastrointestinal Tract in Dogs. G. M. Cummins, M.S., M.D., M. I. Grossman, Ph.D., M.D., and A. C. Ivy, Ph.D., M.D.

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ANNOUNCEMENT

Information Regarding Post-Graduate Instruction in Gastroenterology

At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

Those who are interested in obtaining such instruction should write promptly to the person or school of their choice, because in most instances the number of students who can be accommodated is limited.

Name	*Place*
Aaron, A. H.	Buffalo, N. Y.
Atkinson, Arthur	Passavant Hospital, Chicago
Balfour, Donald	Mayo Clinic
Benedict, Edward B.	Harvard Medical School
Bockus, Henry L.	Univ. of Pennsylvania
Carey, James B.	The Nicollet Clinic, Minneapolis
Crohn, Burrill B.	New York
Garbat, A. L.	Lenox Hill Hospital, N. Y.
Gray, Irving	Brooklyn
Gorham, L. W.	Union University, Albany, N. Y.
Hardt, Leo L.	Chicago
Hollander, Franklin	Mount Sinai Hospital, New York
Ivy, A. C.	University of Illinois
Laing, Grant H.	Chicago
Layne, John A.	Great Falls Clinic, Montana
, John G.	Henry Ford Hospital, Detroit
Wm. S.	University of Rochester
J. C.	Royal Victoria Hospital, Montreal
Miller, T. Grier	Univ. of Pennsylvania
Moser, Rollin H.	Indianapolis
Necheles, H.	Michael Reese Hospital, Chicago
Palmer, Walter L	University of Chicago
Patterson, Cecil O.	Dallas, Texas
Perry, Thomas M.	Georgetown Univ., Wash., D. C.
Pollard, H. M.	Ann Arbor, Mich.
Rafsky, H. A.	Lenox Hill Hospital, N. Y
Rehfuss, Martin E.	Jefferson Med. College
Renshaw, R. J. F.	Cleveland Clinic
Ruffin, Julian M.	Duke University
Silverman, Daniel N.	New Orleans, La.
Sydenstricker, V. P.	University of Georgia
Twiss, J. R.	Post Grad. Med. School, New York
Watson, C. J.	University of Minnesota
Wilkinson, S. Allen	Lahey Clinic, Boston
Willard, John H.	Abingdon Memorial, Abingdon, Pa.
Wood, W. Barry	Washington Univ., St. Louis